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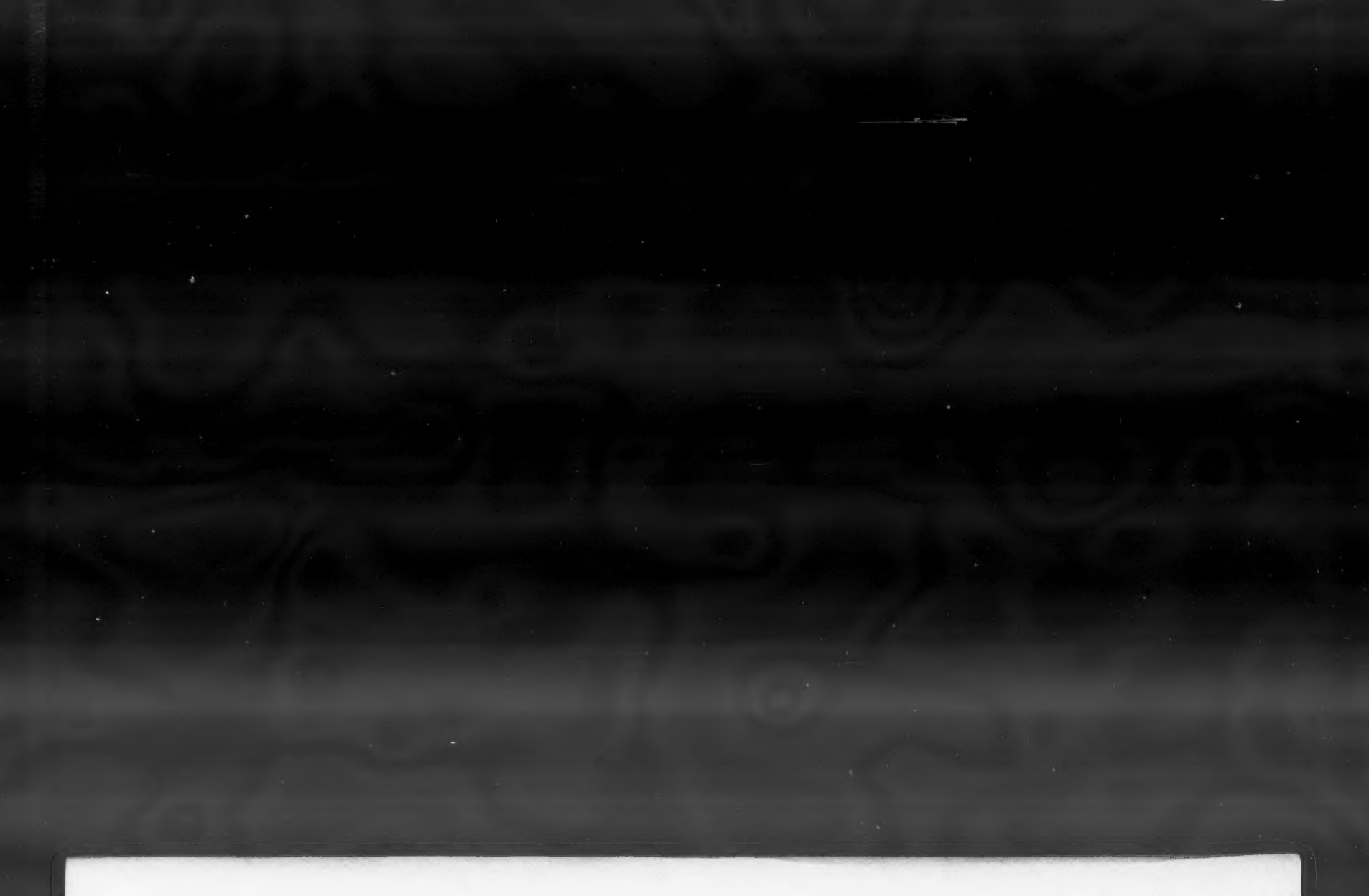

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THE EFFECT OF CORTISONE UPON THE REACTION OF THE SKIN TO TUBERCULIN IN TUBERCULOSIS AND IN SARCOIDOSIS[1]

By K. M. CITRON and J. G. SCADDING

(From the Institute of Diseases of the Chest and Brompton Hospital, London)

Reports concerning the effects of cortisone and corticotrophin upon the reaction of the skin to tuberculin differ widely. Systemic administration of these hormones to selected patients sensitive to tuberculin, but not suffering from active tuberculosis, was found to produce diminution of the tuberculin reaction by Lovell, Goodman, Hudson, Armitage, and Pickering (1953), and by Long and Favour (1950), but unaltered or sometimes diminished reactions were reported by Carey, Harvey, Howard, and Winkenwerder (1950), and by Fischel (1950); both increased and diminished responses were recorded by Coste, Pierre-Bourgeois, Galmiche, Vic-Dupont, Mollon, Nahel, and Blatrix (1951), and by Sulzberger, Sauer, Herrmann, Baer, and Milberg (1951). In patients with active tuberculosis LeMaistre, Tompsett, Muschenheim, Moore, and McDermott (1951) found inhibition or depression of the tuberculin reaction, but Wallner, Thompson, and Lichtenstein (1952) found the reaction unchanged or diminished. The admixture of cortisone with the tuberculin used for an intradermal test was found to produce a smaller reaction than that produced by tuberculin alone by Vollmer (1951) and by Pyke and Scadding (1952). Goldman, Preston, Rockwell, and Baskett (1952), using a similar method, reported that cortisone did not inhibit tuberculin reactions, but hydrocortisone did. Tuberculin sensitivity is depressed in guinea-pigs by systemic cortisone or adrenocorticotrophic hormone (Long and Miles, 1950; Gell and Hinde, 1951; Osgood and Favour, 1951; Derbes, Dent, Weaver, and Vaughan, 1950; Sheldon, Cummings, and Evans, 1950; Harris and Harris, 1950) and by hydrocortisone (Long and Spensley, 1954).

Thus it has usually been found that the tuberculin reaction is inhibited, diminished, or unchanged by cortisone. In contrast to this finding Pyke and Scadding (1952) observed that some patients with sarcoidosis, who were insensitive to tuberculin, reacted to tuberculin while they were receiving cortisone, or if cortisone were mixed with the tuberculin injected intradermally. To elucidate this apparently paradoxical effect of cortisone in sarcoidosis, we have

[1] Received September 22, 1956.

investigated the action of cortisone injected locally with the tuberculin used for intradermal tests in four groups of subjects:

1. Sixty-six patients with pulmonary tuberculosis.
2. Eleven healthy tuberculin-insensitive subjects.
3. Sixteen tuberculous patients rendered insensitive to tuberculin by desensitization with tuberculin.
4. Forty-nine patients with sarcoidosis.

Method

Each subject received four intradermal injections consisting of (1) tuberculin, (2) tuberculin plus cortisone acetate suspension, and controls of (3) cortisone and of (4) the aqueous vehicle in which cortisone is suspended. The method was that previously used by Pyke and Scadding (1952). The tuberculin used was the purified protein derivative (PPD) supplied by the Ministry of Agriculture Veterinary Research Laboratory, Weybridge. 0·00002 mg. PPD is equivalent to one tuberculin unit (TU). Dilutions were prepared freshly every four weeks, and stored at 4° C. They were made up to contain 1, 2, 5, 10, and 100 TU in each 0·05 ml. This volume, mixed with 0·05 mg. of Merck cortisone acetate suspension, containing 1·25 mg. of cortisone acetate, constituted the 'tuberculin plus cortisone' injection. The tuberculin injection was made up by adding 0·05 ml. of the appropriate tuberculin dilution to 0·05 ml. of the aqueous vehicle. The control injections consisted of 0·05 ml. of cortisone acetate suspension with 0·05 ml. of physiological saline solution, and of 0·05 ml. of the aqueous vehicle with 0·05 ml. of physiological saline solution. Thus each injection contained 0·05 ml. of the aqueous vehicle; this appeared important, since the aqueous vehicle contains a surface-active agent and carboxy-methylcellulose, which might conceivably affect the reaction of the skin. A siliconed tuberculin syringe was labelled and reserved exclusively for each of the injections. Since induration could be measured more accurately than erythema, and was often oval rather than circular in shape, the sizes of the tuberculin reactions are expressed in the following analysis as the means of the maximum and minimum diameters of the induration. None of the 142 subjects in this investigation showed any significant reaction to the control injections of cortisone acetate and of aqueous vehicle. At the site of the cortisone injection there might be some oedema at 24 hours, but this invariably resolved at 48 hours, leaving, in some subjects, a nodule not larger than 3×3 mm., presumably due to the particulate nature of the cortisone.

Results in Tuberculous Patients

This group consisted of 66 adults who were in hospital under treatment for active pulmonary tuberculosis. Preliminary intradermal tests with graded doses of tuberculin were performed in the usual way. These tests showed a wide range

of tuberculin sensitivity. According to the degree of sensitivity thus determined, a dose of tuberculin which would produce a reaction between 5 and 20 mm. in diameter was selected from the range 1, 2, 5, 10, and 100 TU for the cortisone-tuberculin tests. The results are shown in Fig. 1, which is a dot diagram in which the abscissa is the mean diameter of the induration caused by tuberculin alone, and the ordinate that of the reaction to tuberculin plus

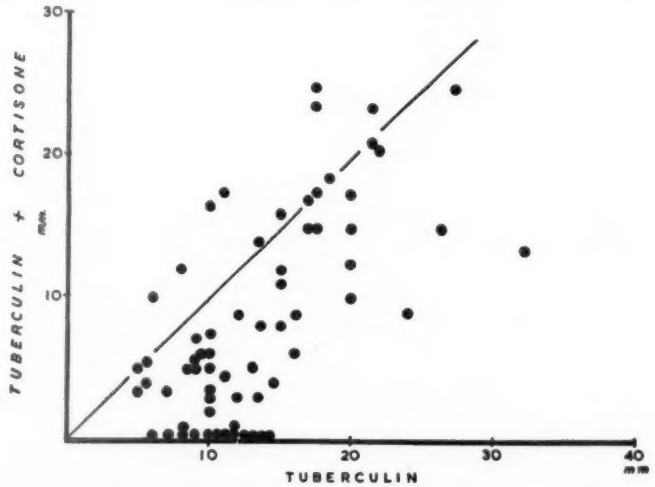

FIG. 1. Reactions to tuberculin and to tuberculin plus cortisone in 66 patients with pulmonary tuberculosis and various tuberculin sensitivities.

In this and subsequent figures the size of each reaction is expressed as the mean of its maximum and minimum diameters.

cortisone. Each point in the diagram represents the reaction to tuberculin alone, and to tuberculin plus cortisone, for one patient. It is evident that the effect of cortisone was not constant. Most reactions were diminished in size by cortisone, some were completely inhibited, several were unchanged, and several were slightly increased. It seemed possible that the degree of inhibition by cortisone could be correlated with either (1) the size of the reaction or (2) the dose of tuberculin used to produce it, or with both these factors.

Effect of size of reaction. Lovell, Goodman, Hudson, Armitage, and Pickering (1953) investigated the effect of cortisone, given systemically, upon tuberculin reactions of different sizes produced by graded doses of tuberculin in the same subject. They found that the differences between the diameters of the reactions produced before and during hormone administration were approximately the same for the various doses of tuberculin used. We have investigated the effect of cortisone, administered locally by our method, upon tuberculin reactions of widely different sizes produced by three graded doses of tuberculin in each of nine tuberculous subjects. We found that cortisone reduced the diameters of large reactions rather less than that of small ones. It seems likely that this slight

difference between our observations and those of Lovell, Goodman, Hudson, Armitage, and Pickering (1953) can be explained by the limited area of skin affected by the cortisone administered locally, as compared with the effect upon the whole skin of cortisone administered systemically. But within the limits of size of reaction used in our main investigation, the influence of size of reaction upon the effect of cortisone, as estimated by the differences between the diameters

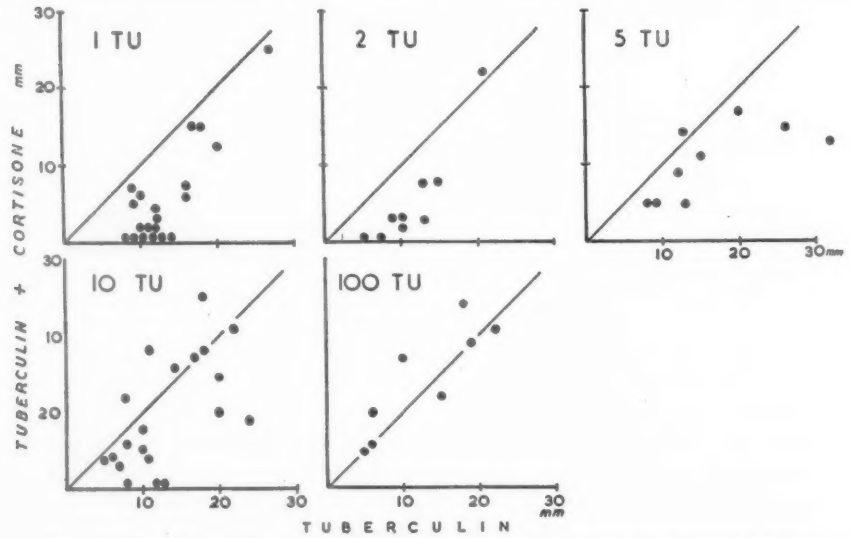

FIG. 2. The data of Fig. 1 presented separately for each level of tuberculin sensitivity, that is, for the patients who reacted to 1, 2, 5, 10, and 100 TU.

of the tuberculin and tuberculin plus cortisone reactions, was slight. We may conclude that the wide scatter of results shown in Fig. 1 cannot be explained as due to a variation of cortisone effect with size of reaction.

Effect of dose of tuberculin. In contrast, if the data obtained in the 66 tuberculous patients of widely differing tuberculin sensitivity are plotted separately for each dose group (1, 2, 5, 10, and 100 TU), important differences become evident (Fig. 2). The larger the dose of tuberculin the less is the effect of cortisone in reducing the reaction, the trend being shown progressively as the dose is increased. Since the mean size of reaction is very similar in each dose group, the influence of size of reaction is negligible, and the grouping by dose of tuberculin is also in a general way a grouping by tuberculin sensitivity. We may say, therefore, that the inhibitory effect of cortisone upon the tuberculin reaction diminishes with diminishing tuberculin sensitivity.

Results in Other Groups

Healthy tuberculin-insensitive subjects. Tests were performed, using 100 TU, on 11 healthy subjects who gave no reaction to this dose of tuberculin (Fig. 3).

None gave any appreciable reaction to tuberculin plus cortisone, the largest being a nodule 3×3 mm. Thus no significant reactions to tuberculin plus cortisone were observed in uninfected healthy subjects.

Desensitized tuberculous patients. This group consisted of 16 patients with active pulmonary tuberculosis, all initially highly sensitive to tuberculin, who had been desensitized to tuberculin, as an adjunct to chemotherapy, by the

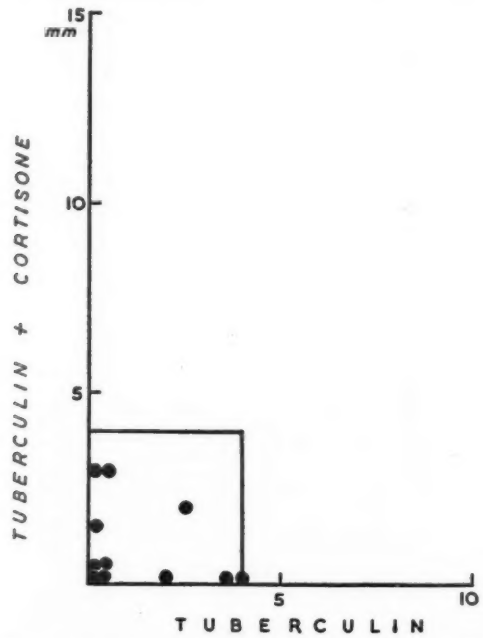

FIG. 3. Reactions to 100 TU of tuberculin, and to the same dose of tuberculin plus cortisone, in 11 healthy tuberculin-insensitive subjects.

intramuscular injection of increasing doses of tuberculin until the skin failed to react to 100 TU. Results of tests upon these patients, using 100 TU, are shown in Fig. 4. Eleven of the 16 patients (70 per cent.) gave a reaction of more than 4 mm. in response to tuberculin plus cortisone, while none of the 11 gave any reaction to tuberculin alone. This result contrasts with the absence of response to tuberculin plus cortisone in the healthy tuberculin-negative control subjects (Fig 3).

Patients with sarcoidosis. In making the diagnosis of sarcoidosis we have adhered to the definition suggested by Scadding (1950). The observations reported by Pyke and Scadding (1952) in 12 patients have been confirmed in 49 additional patients with sarcoidosis. In 80 per cent. of these patients histological confirmation of the diagnosis was obtained. Pulmonary infiltration was present in 92 per cent., and hilar lymph-node enlargement in 53 per cent. Twenty-eight patients failed to react to at least 100 TU. The results of tests on

these patients (using 100 TU or, in six cases, 1,000 TU) are shown in Fig. 5. Fourteen patients out of 28 (50 per cent.) gave a reaction of more than 4 mm. in response to tuberculin plus cortisone. This result is to be compared with a similar reaction in 70 per cent. of the desensitized tuberculous patients (Fig. 4), and the absence of reactions in healthy tuberculin-insensitive subjects (Fig. 3). Of the patients who were sensitive to tuberculin, 15 reacted only to 100 TU or

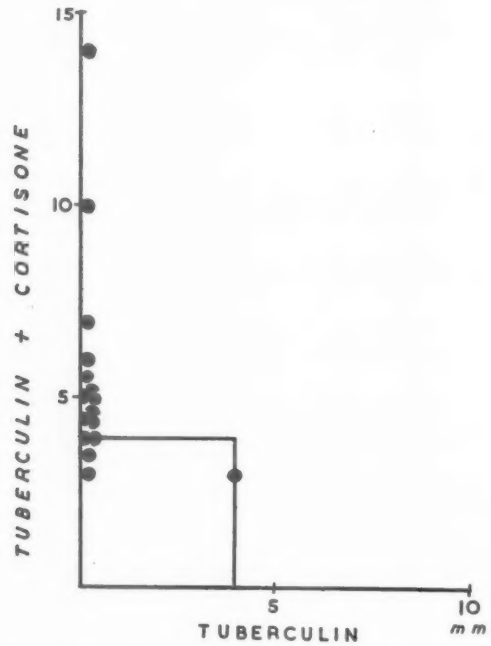

FIG. 4. Reactions to 100 TU of tuberculin, and to the same dose of tuberculin plus cortisone, in 16 patients with pulmonary tuberculosis who had been desensitized to tuberculin.

larger doses. Results of tests upon these patients are shown in Fig. 6; they are very similar to those obtained in tuberculous patients of similar sensitivity, shown in Fig. 2. In both groups the reaction was, in general, unaltered by the addition of cortisone.

Analysis of Results

The influence of cortisone upon the tuberculin reaction in the various groups is summarized in Figs. 7 and 8, in which the data are presented in terms of the mean differences between the reactions to tuberculin and to tuberculin plus cortisone for each group. In tuberculous patients (Fig. 7) the inhibitory effect of cortisone is greatest in the low-dose or high-sensitivity group, and diminishes progressively with diminishing sensitivity, until in the 100-TU group cortisone

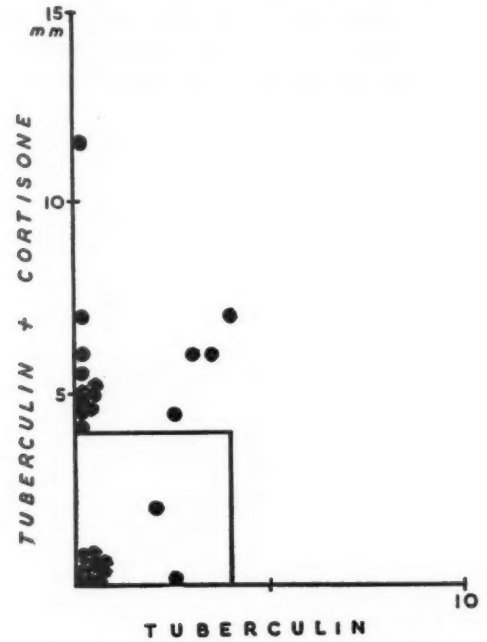

FIG. 5. Reactions to tuberculin, and to tuberculin plus cortisone, in 28 patients with sarcoidosis who did not react to tuberculin alone.

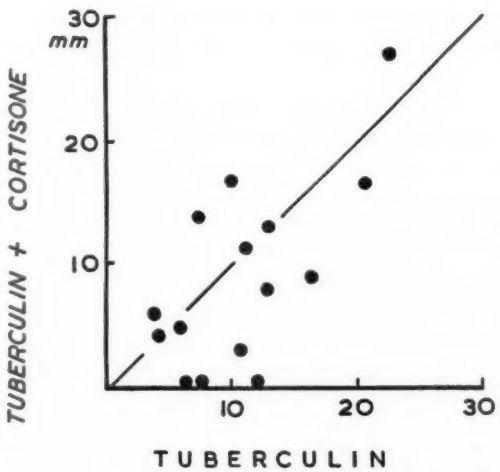

FIG. 6. Reactions to tuberculin, and to tuberculin plus cortisone, in 15 patients with sarcoidosis who reacted to tuberculin in a dosage of 100 TU or more.

has no significant effect. The differences are significant at the 1 per cent. level for the 1-TU and 2-TU groups, and at the 5 per cent. level for the 5-TU and 10-TU groups. In the tuberculin-positive sarcoidosis group (Fig. 8), as in the low-sensitivity tuberculous group, there is no significant effect of cortisone.

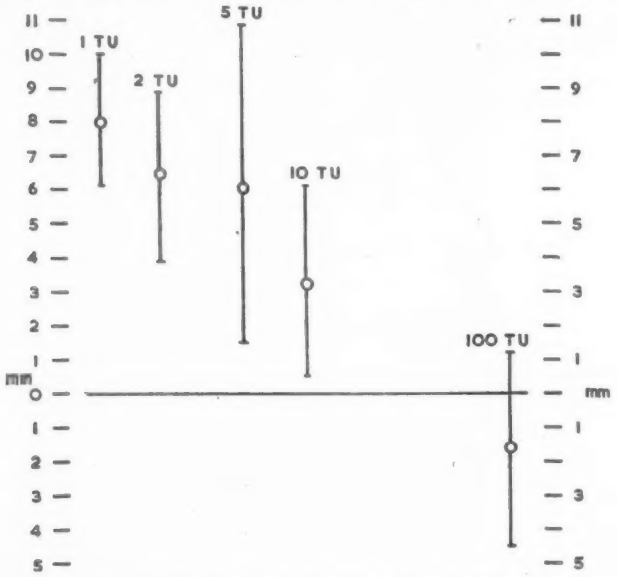

FIG. 7. The data of Fig. 2 presented as the means of differences between reactions to tuberculin and to tuberculin plus cortisone, with 95 per cent. confidence limits.

In the tuberculin-insensitive sarcoidosis group and in the desensitized tuberculous group the effect of cortisone is to induce a reaction to tuberculin in some cases.

The specificity of the local action of cortisone upon the tuberculin reaction. Non-specific factors, including local irritation, may inhibit or enhance tuberculin reactions by altering local vascular response (Pepys, 1955). It was necessary, therefore, to determine whether the observed effects of cortisone were specific, or due to non-specific irritation by the particulate cortisone acetate suspension. That the effects of cortisone were specific is shown by three observations.

1. Cortisone given systemically has been found to induce tuberculin reactions in some patients with sarcoidosis who are insensitive to tuberculin (Pyke and Scadding, 1952), and has been found to inhibit or diminish tuberculin reactions in non-tuberculous and tuberculous subjects (Lovell, Goodman, Hudson, Armitage, and Pickering, 1953; LeMaistre, Tompsett, Muschenheim, Moore, and McDermott, 1951).

2. The possibility that the particulate cortisone suspension might, by non-specific irritation, affect the tuberculin reaction, was investigated by substituting a suspension of cholesterol of the same particle size and concentration for the

cortisone acetate. The cholesterol was found to have no inhibitory effect upon the reactions produced by doses of 5 and 10 TU in 11 tuberculin-sensitive subjects. The mean diameter of the reactions to tuberculin plus cholesterol was in fact slightly greater than that of the reactions to tuberculin alone, the mean increase being 3·0 mm. (standard error $\pm 1{\cdot}4$).

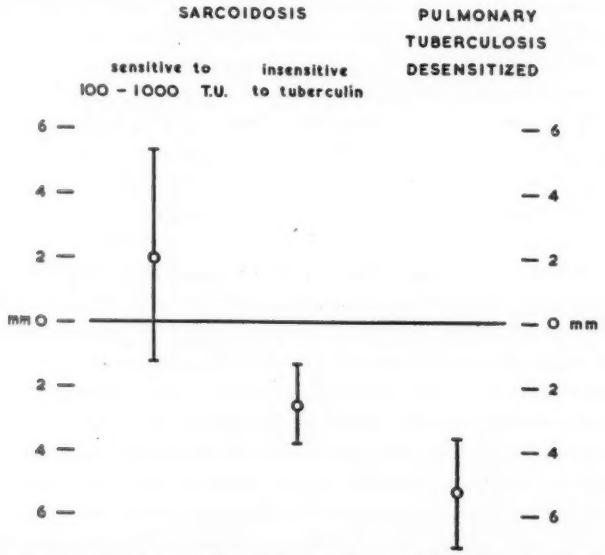

FIG. 8. The data of Figs. 4, 5, and 6 presented as the means of differences between reactions to tuberculin and to tuberculin plus cortisone, with 95 per cent. confidence limits.

3. A non-particulate preparation of hydrocortisone, in a water-soluble vehicle containing 0·1 mg. of the steroid, was injected with 5 or 10 TU in 12 subjects. A highly significant reduction of the tuberculin reaction was obtained, the mean change in induration being $-6{\cdot}8$ mm. (standard error $\pm 1{\cdot}6$), significant at the 1 per cent. level.

Discussion

The observation that the effect of cortisone upon skin reactions to tuberculin is graded, from strong inhibition of reactions produced by small doses in subjects of high sensitivity, to no inhibition of those produced by large doses in subjects of low sensitivity, may serve to explain the apparently discrepant reports which have been made in the past, but is itself difficult to explain. Does this gradation of inhibition by cortisone assist in explaining the observation that some patients with sarcoidosis, and desensitized tuberculous patients, who do not react to tuberculin alone, react to tuberculin plus cortisone? Cortisone induces no reaction in healthy tuberculin-insensitive subjects when added to tuberculin in an intradermal test. Thus, patients with sarcoidosis react like tuberculous patients who have been desensitized, and differently from healthy

tuberculin-insensitive subjects. It seems possible that, in both the desensitized tuberculous and the sarcoidosis patients, there is a residuum of tuberculin sensitivity too slight to be detected by tuberculin alone, and that the addition of cortisone in some way enables this to be detected.

The tuberculin reaction is influenced by three factors: first, the local concentration and retention at the site of injection of the antigen tuberculin; second, the ingress into the challenged site of leucocytes which carry the antibody; third, the reactivity of the tissues. Prolonging the period of retention of tuberculin at the site of injection might enable sufficient antibody to be brought to the site by circulating leucocytes, even though each carried very little antibody, to permit a reaction to develop before the tuberculin had diffused away. The fact that increasing the local retention of tuberculin does enhance the tuberculin reaction has been simply demonstrated by the use of 'depot' preparations, in which the tuberculin is put up in an oily vehicle to delay its dispersion. It has been shown (Seeberg, 1951; James and Pepys, 1956), and we have confirmed the observation, that many patients with sarcoidosis insensitive to aqueous tuberculin react to depot tuberculin; and we have found that many desensitized tuberculous patients also react to this preparation. Of 11 patients with sarcoidosis insensitive to aqueous tuberculin, nine reacted to tuberculin in oil, and all of five desensitized tuberculous patients reacted. There is evidence to suggest that cortisone, like the oily vehicle, prolongs the retention of tuberculin at the site of injection. Lovell, Scott, Hudson, and Osborne (1953) have shown that cortisone delays the dispersion of bruises in the skin. We have made studies by means of ultra-violet light photography of the influence of 1·25 mg. cortisone acetate, injected locally, upon the spread of fluorescein in the skin, and find that cortisone increases the local retention of this substance. It is reasonable to assume that cortisone also delays the spread of tuberculin in the skin. This would tend to enhance the tuberculin reaction and, like depot tuberculin, permit detection of degrees of tuberculin sensitivity too slight to be detected by aqueous tuberculin. On the other hand, the anti-inflammatory effect of cortisone would be expected to suppress the tuberculin reaction by altering the reactivity of the tissues. Allison, Smith, and Wood (1955) have shown that, in thermal inflammation, cortisone produces increased tone of vessels and diminution of hyperaemia. Both the action of cortisone in causing local retention and its anti-inflammatory action can be related to these vascular effects. Allison, Smith, and Wood (1955) also showed that cortisone diminishes diapedesis of leucocytes through capillaries; this would tend to limit the ingress of leucocytes carrying the antibody concerned in the tuberculin reaction to the site of an intradermal test, and thus would be expected to diminish the reaction. The apparently paradoxical effect of cortisone in inducing tuberculin reactions under some conditions, while inhibiting them under others, may be explicable as a result of varying preponderance of these various factors. In subjects of low sensitivity we have shown that cortisone has little or no inhibitory effect upon the skin reactions caused by relatively large doses of tuberculin. Patients with sarcoidosis who react to tuberculin plus cortisone may be extreme examples of low

tuberculin sensitivity, so that in them the anti-inflammatory effect is subordinate to the tuberculin-retaining effect.

The interpretation of our observations in relation to the vexed problem of the aetiology of sarcoidosis is by no means simple. The high incidence of negative reactors to tuberculin is generally interpreted, by those who believe that sarcoidosis is not causally related to tuberculosis, as due to non-specific depression of tissue reactivity, similar to that which is observed in Hodgkin's disease and other reticuloses (Hoyle, Dawson, and Mather, 1954). On the other hand, those who hold that sarcoidosis is, at least in some instances, a manifestation of tuberculosis, regard the failure to react to tuberculin as a feature of the peculiar tissue reactivity which determines the development of sarcoidosis in response to tuberculous infection. Superficially, the suggested explanation of the paradoxical effect of cortisone in tuberculin-negative sarcoidosis which we have made above, that it unmasks a very low degree of tuberculin sensitivity, appears to be equally consonant with either of these views. Of the 49 patients with sarcoidosis whom we investigated, 71 per cent. showed some degree of tuberculin sensitivity, if the number reacting to tuberculin plus cortisone is added to those reacting to tuberculin alone. The fact that this figure approximates to the generally observed proportion of reactors to tuberculin in the general population might appear to support the view that the depression of tuberculin sensitivity in sarcoidosis is non-specific. Analysis, however, of the incidence of evidence of old tuberculosis in the sarcoidosis patients shows that this simple view is untenable. Of the 14 patients with sarcoidosis who failed to react either to tuberculin or to tuberculin plus cortisone, seven had clear evidence of previous tuberculous infection. Of these seven patients, six had calcified foci in the lung or hilar lymph-nodes, and three had previously had tubercle bacilli of human type in the sputum. Among the 14 who failed to react to tuberculin, but reacted to tuberculin plus cortisone, four showed calcification, and one had on one occasion produced tubercle bacilli. There was thus no correlation between evidence of old tuberculous infection and a positive reaction to tuberculin plus cortisone in the sarcoidosis patients who failed to react to tuberculin alone. If sarcoidosis is unrelated to tuberculosis, except that it depresses tuberculin sensitivity in those who happen to have been infected previously with tubercle bacilli, a strong correlation would be expected between these two findings. On the other hand, if sarcoidosis is a peculiar manifestation of tuberculosis, in which low tuberculin sensitivity is part of the unusual tissue reactivity which determines the development of the characteristic histological pattern, it would not be surprising to find that there was no such correlation.

In caseating tuberculosis the range of tuberculin sensitivity is wide and, even in the absence of such well-recognized factors as extreme illness and intercurrent disease, the tuberculin reaction, even to 100 TU, may be negative (Mascher, 1951; Scadding, 1956). In sarcoidosis also the range of tuberculin sensitivity is wide, though on a generally lower level. A procedure which permits the detection of a very low degree of tuberculin sensitivity would, therefore, be expected to produce variable results in sarcoidosis; and if all the cases of

sarcoidosis examined were of tuberculous aetiology, there would be no reason to expect that those who happen to show radiological evidence of the caseating phase of the disease would tend, more than the rest, to show evidence of residual tuberculin sensitivity. For these reasons we think that our observations favour the view that in most, if not all, of our patients sarcoidosis was a manifestation of tuberculosis.

Among the tuberculin-insensitive sarcoidosis patients, those who gave reactions to tuberculin plus cortisone constitute about 50 per cent., a figure similar to that previously observed in a smaller series by Pyke and Scadding (1952). We have not observed a reaction to tuberculin plus cortisone in a subject failing to react to tuberculin alone, except in patients with sarcoidosis and patients with tuberculosis who had been desensitized to tuberculin. An intradermal test with tuberculin plus cortisone therefore appears to be of some diagnostic value in Mantoux-negative subjects suspected to be suffering from sarcoidosis. A negative result is of no significance, but a positive result would favour the diagnosis of sarcoidosis.

We are grateful to Dr. P. Armitage and Mr. P. Payne for statistical advice; to the patients and normal subjects for their co-operation in the skin tests; to Drs. J. L. Livingstone, D. G. Madigan, H. Nicholson, N. C. Oswald, and F. H. Young for allowing us access to patients under their care; and to Dr. J. R. Bignall for much critical discussion. The cortisone was provided by the Medical Research Council. The non-particulate preparation of hydrocortisone was supplied by Roussel Laboratories Ltd.

Summary

The influence of cortisone upon the reaction of the skin to tuberculin has been investigated by simultaneous intradermal tests with tuberculin and with tuberculin mixed with cortisone acetate suspension.

In active pulmonary tuberculosis the action of cortisone upon the size of tuberculin reactions was variable. In subjects of high tuberculin sensitivity reactions were reduced in size or inhibited; but the inhibitory effect diminished progressively with diminishing tuberculin sensitivity, until in subjects of low sensitivity the size of reactions produced by 100 TU was unchanged. In healthy tuberculin-insensitive subjects tuberculin plus cortisone caused no reaction. In tuberculous patients whose skin had been rendered insensitive to tuberculin by desensitization with tuberculin, tuberculin plus cortisone induced reactions in 70 per cent. of cases. A previous observation, that tuberculin plus cortisone induced reactions in 50 per cent. of patients with sarcoidosis who were insensitive to tuberculin, was confirmed.

These results suggest that cortisone, possibly by its effect in prolonging the retention of tuberculin at the site of injection, permits the detection of a degree of tuberculin sensitivity too low to be detected by tuberculin alone. Among the 28 patients with sarcoidosis who failed to react to tuberculin, of whom 14

reacted to tuberculin plus cortisone, 12 had radiological or bacteriological evidence of old tuberculosis; and there was no correlation between a reaction to tuberculin plus cortisone and other evidence of tuberculosis. These observations support the view that there is a causal rather than a casual relationship between tuberculosis and sarcoidosis in the patients investigated.

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VENO-OCCLUSIVE DISEASE OF THE LIVER[1]

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With Plates 27 to 31

A recently recognized syndrome occurring in the West Indies has been called veno-occlusive disease of the liver. The term was suggested by the very characteristic histological picture, which has been described in previous papers (Bras, Jelliffe, and Stuart, 1954*a*, *b*). Clinical accounts of the disease in Jamaican children (Rhodes, 1954; Jelliffe, Bras, and Stuart, 1954; Stuart, 1955) and adults (Stuart and Bras, 1955) have also been given. The disease has probably occurred in Jamaica, at any rate, for several years; and although detailed histological studies were not undertaken, the reports of McFarlane and Branday (1945) and Royes (1948) probably refer to this syndrome. Its occurrence in Barbados, another West Indian island, has been reported recently (Stuart and Bras, 1956). By relating the results of serial liver biopsies to the clinical and biochemical findings at progressive points in the disease, it has been possible to define three often ill-defined and overlapping stages (Fig. 1).

A. *Acute Veno-occlusive Disease*

The initial acute phase is characterized by the rapid development of abdominal discomfort, a smooth, firm, and often gross hepatomegaly, and usually considerable ascites. Nausea and vomiting are common but usually unobtrusive complaints. Slight splenomegaly and oedema, usually confined to the lower limbs, sometimes occur. The highest incidence is between 12 months and six years of age, but the disease also occurs in all other age-groups (see p. 302, Fig. 2). Sometimes two or more children in one family, and occasionally all, are affected, frequently within days or weeks of each other. The condition is often precipitated by illnesses such as whooping-cough or other respiratory infections. Some patients make a complete clinical recovery, the results of liver function tests and liver biopsy becoming normal; but a number die in the acute phase of liver failure and, occasionally, intercurrent infection. Jaundice sometimes occurs in the acute or later stages of the disease. Pleural effusions, often massive, are not uncommon. The acute phase may pass, often imperceptibly, into the subacute stage, or the disease may be subacute from the onset.

[1] Received September 12, 1956.

Case Histories

The liver function tests and biopsy findings in the 10 cases reported in this paper are shown in Table I (p. 299).

Case 1. C. D., a two-and-a-half-year-old Jamaican girl, was admitted to hospital in May 1955. She had been quite well up to two weeks before admission, when she developed a mild upper respiratory infection, with cough and low-grade pyrexia for a few days. Her abdomen soon afterwards became distended,

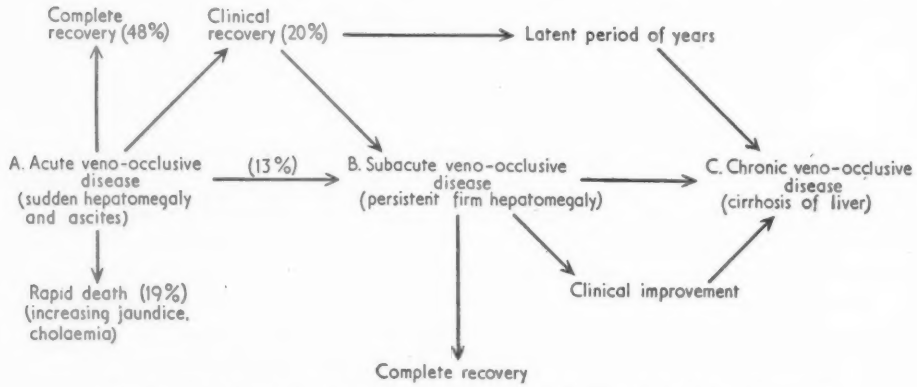
Complete recovery (48%)
Clinical recovery (20%)
Latent period of years
A. Acute veno-occlusive disease (sudden hepatomegaly and ascites)
(13%)
B. Subacute veno-occlusive disease (persistent firm hepatomegaly)
C. Chronic veno-occlusive disease (cirrhosis of liver)
Rapid death (19%) (increasing jaundice, cholaemia)
Clinical improvement
Complete recovery

FIG. 1. Clinical natural history of veno-occlusive disease of the liver. B and C may be present with no clinical history of preceding illness.

and she complained of abdominal pain and discomfort, and lost her appetite. A detailed dietary history could not be obtained. Clinically she was well-nourished, and the main findings on examination were a tense ascites, a firm, smooth enlargement of the liver to about 1 cm. below the umbilicus, and a large right pleural effusion found on clinical and X-ray examination. There was no jaundice, and the temperature was normal. Apart from the liver function tests (Table I), the results of all other special investigations were negative. Pleural and abdominal paracenteses were necessary soon after admission, and three further abdominal paracenteses were required in the next four weeks, after which the hepatomegaly and ascites gradually subsided, the general condition improved, and the results of liver function tests became normal. She was discharged clinically well 58 days after admission. She has been followed up in the out-patient department for over 12 months, and has remained well.

A liver biopsy was done on admission, and repeated four weeks later when she was clinically normal. The first biopsy (S/55/686) showed the typical picture of acute veno-occlusive disease of the liver. There was occlusion of the smaller hepatic veins, as described by Bras, Jelliffe, and Stuart (1954*a*) and Bras and Hill (1956). The centrilobular areas were congested, and the centrilobular liver-cells had almost completely perished, those which remained showing fatty metamorphosis. The reticulum framework in the centrilobular areas was collapsed. The periportal areas showed no remarkable change (Plate 27, Fig. 5). The second biopsy (S/55/896) was entirely normal, and showed no residual change (Plate 27, Fig. 6).

Diagnosis. Acute veno-occlusive disease with complete clinical, biochemical, and histological recovery.

Case 2. R. L., a three-year-old Jamaican boy, was admitted to hospital in February 1955. One week before admission he complained of abdominal pain, and a few days later his abdomen became distended, and swelling of the feet was noticed. There was no previous history of any significant illness. His diet had been the usual high-carbohydrate Jamaican diet, with a relative deficiency of fat and protein. There was in addition the customary variety of 'bush teas' (infusions of local herbs and roots). His nutritional state on admission was fairly good. The temperature was 102° F., the pulse 140, and the respirations 40 per minute. There was pitting oedema of the ankles and legs up to the knees, and there were the clinical features of a large right pleural effusion. The liver was enlarged to the umbilicus, and there was a tense ascites. Apart from the chest X-ray, which showed a large right pleural effusion with mediastinal displacement, and the liver function tests (Table I), other special investigations, including full haematological examination and tests for sickling, serological tests for syphilis, the Mantoux test, and examination of ascitic and pleural fluid for tubercle bacilli, were entirely negative. Treatment was started with penicillin, mersalyl, restricted salt and fluid intake, and a high-protein diet. Abdominal and thoracic paracenteses were again necessary soon after admission because of increasing respiratory distress. The pleural fluid (24 ounces) showed a remarkably high protein-content, containing a total of 18·9 gm. per 100 ml. (albumin 11·6 gm. and globulin 7·3 gm.). The protein-content of the ascitic fluid was not abnormally high. Improvement thereafter was rapid. The temperature settled in 24 hours, the appetite improved, and chest X-rays 14 and 28 days afterwards were normal. No further abdominal paracenteses were required. The child was discharged well, without hepatomegaly or ascites, and with normal results from liver function tests, 10 weeks after admission. He has remained well under out-patient observation up to the time of writing.

Liver biopsies were performed on admission, one month afterwards when there was marked clinical improvement but still some hepatomegaly, and again shortly before discharge when the hepatomegaly and ascites had disappeared. The first biopsy (S/55/212) showed the typical picture of acute veno-occlusive disease (see Case 1). The second biopsy (S/55/319) still showed a pericentral congestion and necrosis which, however, were greatly diminished in amount. The third biopsy (S/55/469), performed two months after the first, showed complete disappearance of all congestion, with no residual fibrosis or any other remarkable change.

Diagnosis. Acute veno-occlusive disease with full recovery.

Case 3. C. B., a man of 33 years, first attended University College Hospital in December 1953, with a complaint of cough and occasional pain in the chest for the previous four months. He had always taken a variety of 'bush teas', and at the onset of his illness he had added a number of others for their supposed medicinal value in the treatment of cough. On physical examination he was found entirely normal, but he was kept under observation as an out-patient because chest X-rays had shown changes suggesting partial collapse of the right middle lobe. Liver function tests gave normal results, and repeated examinations of sputum for tubercle bacilli were negative. In March 1954, nine weeks after his first visit and one week after his last out-patient visit, he attended hospital complaining of abdominal pain, anorexia, and occasional vomiting for the past two days. He had no fever, but was obviously ill. There was a tense ascites, and the liver was tender and enlarged as far as the umbilicus. The spleen could not be felt. There was no anaemia, jaundice, or oedema. Tests on admission showed impaired liver function (Table I), but the other laboratory investigations,

including haematological examination and tests for sickling, serological tests for syphilis, and blood electrolytes, were normal. Chest X-rays showed no change from the previous examination. In spite of treatment as given in Case 2, the hepatomegaly and ascites persisted, and five paracenteses were required in the next six weeks. Liver function tests showed further deterioration (Fig. 3). A liver biopsy (S/54/431) at this stage showed the changes of acute veno-occlusive disease. After six weeks the ascitic fluid ceased to accumulate, the patient became clinically free of ascites in 10 days, and the hepatomegaly disappeared completely in 21 days. There was a parallel improvement in symptoms and in the liver function tests. He was discharged well 10 weeks after admission, and readmitted three weeks later for a second liver biopsy (S/54/729), which showed no residual histopathological changes. His course since discharge, under out-patient observation, has been uneventful.

Diagnosis. Acute veno-occlusive disease in an adult, with full recovery.

Case 4. L. E., a 14-month-old child, was admitted to hospital in May 1953, with a three-day history of abdominal swelling, loss of appetite, and occasional vomiting. His mother had also noticed swelling of the lower limbs 24 hours before admission. He had been breast-fed up to nine months of age, when he was weaned on a diet of oatmeal porridge, carrot juice, and an assortment of local 'bush teas'. He had been well until his illness started. He appeared a well-nourished child. The liver was enlarged to within an inch of the umbilicus, but not tender. There was oedema of the feet, but only a moderate degree of ascites, at the time of examination. The only other abnormal finding was an icteric tinge of the sclera. Liver function tests showed marked impairment. Within a few days of admission the jaundice rapidly deepened, and the child gradually became listless, apathetic, and drowsy. He died deeply jaundiced, and with hepatic coma, 14 days after admission. Liver biopsy was not performed.

Post-mortem examination (P.M. 96). The body-height was 70 cm., and weight 8·6 kg. The liver weighed 235 gm. The surface was smooth, glistening, transparent, and lightly bile-stained. There were collateral vessels running between the domes of both lobes and the diaphragm, and the ligamentum teres contained patent blood-vessels. The cut surface was mottled, and had the characteristic nutmeg appearance described in acute veno-occlusive disease (Bras, Jelliffe, and Stuart, 1954*b*; Bras and Hill, 1956). The vena cava and the larger hepatic veins showed no evidence of occlusion. The medium-sized hepatic veins were found to have swelling of the intima, slightly gelatinous in gross appearance, and partly or completely occluding the lumen. Histological examination showed acute veno-occlusive disease, but more severe than that described in the previous patients. There was marked necrosis of the centrilobular liver-cells.

Diagnosis. Acute veno-occlusive disease with death in hepatic failure.

Case 5. First admission. R. B. (Plate 28, Fig. 7), a two-year-old Jamaican boy, was admitted to hospital in October 1954. One week before admission he developed a cough with fever, and three days later his abdomen and legs began to swell, and rapidly increased in size. There was considerable anorexia, and some vomiting, the week before admission. On admission the temperature was 98·0° F., the pulse 140, and respirations 44 per minute. Generalized oedema was conspicuous, and there was scleral jaundice. Tense ascites and oedema of the abdominal wall were present. Many dilated, but not aneurysmal, veins were visible on the abdomen and over the lower chest wall. After paracentesis the liver was found to be enlarged almost to the umbilicus (Plate 28, Fig. 7). The spleen was not palpable. In this case also the laboratory investigations, except

liver function tests, gave normal results. Chest X-rays showed a small right basal effusion. Treatment was started as in the preceding cases. For the next two months there were repeated reaccumulations of ascites, requiring a total of 10 paracenteses. Oedema of the lower limbs recurred with the ascites, and settled after paracentesis. Liver function tests showed further deterioration. There were also episodes of pyrexia up to 102° F., lasting up to 10 days, for which no cause could be demonstrated. No further paracenteses were required after two months, and the ascites, jaundice, and pyrexia gradually cleared. The appetite and general condition then rapidly improved. The spleen became palpable three months after the patient's admission. In spite of clinical and biochemical improvement, serial liver biopsies showed the development of a progressive fibrosis. He was discharged clinically well 19 weeks after admission, but the liver was now very hard, and still enlarged nearly to the umbilicus. The spleen was enlarged to half-way between the costal margin and the umbilicus.

Second admission. He was readmitted in May 1955, two months after his discharge, for reassessment. He had been quite well since leaving hospital, except for a mild pyrexia for a few days before readmission, and, apart from a mild jaundice, the clinical features were essentially unchanged. Liver biopsy and liver function tests were repeated, and he was discharged after 12 days of observation. For the next seven months he was seen in the out-patient department at monthly intervals.

Third admission. Haematemeses occurred for the first time in December 1955, two weeks after his last out-patient visit, and he was again admitted to hospital. An immediate blood transfusion was required, and there was some improvement, but severe haematemesis recurred twice in the next 48 hours. The following day ligation of the left gastric and oesophageal vessels was performed as an emergency operation. His progress for three weeks after operation was stormy; after this there was sustained improvement, without recurrence of haematemesis, for six weeks. A portal venogram at this time (by Dr. Sheila Sherlock on a visit to Jamaica) showed an incomplete obstruction of the portal venous system, with extensive anastomotic circulation. Haematemeses eventually recurred, and an attempt was made to perform a portacaval anastomosis, but this was impossible owing to splenic vein thrombosis. The boy's condition gradually deteriorated, and he died after two massive haematemeses, three months after his third admission and 15 months from the onset of the illness.

Histology and post-mortem findings. The first liver biopsy (S/54/1472) showed the typical picture of veno-occlusive disease of the liver. The second biopsy specimen (S/55/123) was taken eight weeks after the first, and showed a centrilobular fibrosis. The third (S/55/290), taken approximately three months after the first, again showed marked centrilobular fibrosis, while the fourth (S/55/687), taken six months after the first, showed a commencing destruction of the lobular pattern, due to progressive fibrosis. There was evidence of collateral circulation, and the picture had assumed the appearance of a true non-portal cirrhosis. *Post mortem* (P.M. 702) the body was 102 cm. in height, and weighed 13·9 kg. There was no free fluid in the abdominal cavity, but the left pleural cavity contained 250 ml. of straw-coloured fluid. The liver weighed 667 gm. and was pale yellowish-brown. There were many adhesions between the liver and the anterior abdominal wall, diaphragm, colon, and stomach, containing collateral vessels. The edge was sharp, and the surface finely granular. On cross-section the liver presented a cirrhotic pseudolobular appearance. Histological examination showed the typical non-portal cirrhosis described by Bras, Jelliffe, and Stuart (1954*a*, *b*) and Bras and Hill (1956).

Diagnosis. Acute veno-occlusive disease progressing to gross hepatic cirrhosis and death from haematemeses in 15 months.

Case 6. P. D., a 10-month-old Jamaican infant, was admitted to hospital in August 1953, with a four-day history of abdominal distension, anorexia, and slight pyrexia. She had been breast-fed up to six months, when she was weaned on the usual diet containing oatmeal porridge and 'bush teas'. She was a moderately well nourished but rather apathetic child, weighing 7·5 kg. The temperature was 100° F., pulse 130, and respirations 36 per minute. The sclerae were moderately icteric. The abdomen was distended, and free fluid present, and there was a firm, smooth enlargement of the liver to 5 cm. below the costal margin. The spleen was not palpable.

Laboratory studies again gave mostly normal results, but the tests showed impaired liver function, a low-grade anaemia (haemoglobin 9·8 gm. per 100 ml.), a white-cell count of 16,100 per c.mm. with a normal differential count, and a very dark urine containing a large amount of bilirubin but no urobilinogen or urobilin. Treatment was started with skimmed milk, oral glucose, penicillin, and blood transfusion (200 ml.), but the infant's condition gradually deteriorated. Jaundice and apathy increased, and she died in hepatic coma 10 days after admission.

Post-mortem examination (P.M. 138). The height was 63 cm., and the body weighed 7 kg. The liver weighed 280 gm., and was similar in appearance to that seen in Case 4, except that there was more pronounced bile-staining. Histological examination again showed an extensive destruction of the parenchyma in the centrilobular areas, and the picture of acute veno-occlusive disease.

Comment. Acute veno-occlusive disease, very similar in presentation and course to the Indian type of infantile cirrhosis (Rao, 1935–6): that is, hepatomegaly and ascites of sudden onset, progressing rapidly to fatal icteric cholaemia.

B. *Subacute Veno-occlusive Disease*

In the subacute stage there is persistent hepatomegaly, and sometimes splenomegaly (Plate 28, Figs. 8 and 9). There are often recurrences of slight or considerable ascites; but the patient is often free from symptoms, the condition being discovered on routine examination or on examination for an independent complaint. Response to treatment is variable, and slower than in the acute stage. Acute episodes may occur in both the subacute and chronic stages. Complete resolution may occur, but the condition frequently passes, often subclinically, into the chronic stage of the disease (Fig. 1).

Case 7. W. McD. (Plate 28, Fig. 8), a five-year-old boy, was admitted to hospital in November 1952 with a 12-day history of abdominal swelling. There were no other symptoms, and the child had never been ill before. The diet had been mainly carbohydrate, with the usual 'bush teas'. He was a well-built boy, and the only significant findings on admission were a moderate amount of ascites and a firm hepatomegaly. Paracentesis was not required. Liver function tests showed only slight impairment. Improvement was rapid, and on discharge after five weeks' treatment the ascites had disappeared, and the liver was about 2 cm. smaller. Six weeks after his discharge the ascites recurred after a 'cold', with cough and fever, which had been treated at home with 'bush teas'. Examination showed that he had relapsed, the abdomen again being distended with free fluid, while the liver was again enlarged to the umbilicus. Response to treatment

with high-protein diet and restriction of salt and fluid was again rapid. The ascites cleared in two weeks, and he was discharged well, but with the hepatomegaly unchanged, four weeks after admission. He was seen in the out-patient department at intervals for the following 18 months, during which he remained well. When last seen the liver was much smaller, being palpable only 4 cm. below the costal margin, but rather firm in consistency. The results of liver function tests have remained within normal limits, and there has been no recurrence of ascites. Liver biopsies were performed at the beginning and end of both periods in hospital.

Histology. The first biopsy (S/52/199) showed a typical picture of veno-occlusive disease. The second biopsy specimen (S/52/280), taken six weeks after the first, showed that the reticulin condensation in the centrilobular area, which was already present on the first occasion, had advanced, and there was now some proliferation of the reticulin in these areas. Widened sinusoids had developed near obliterated vessels, opposite the areas of densest fibrosis, evidently representing a compensatory collateral circulation. The third (S/53/206) and fourth (S/53/306) biopsies were done 10 weeks and four and a half months respectively after the first, and revealed approximately the same picture as the previous biopsies, except that there was no doubt that the centrilobular fibrosis was steadily progressing towards a true cirrhosis.

Diagnosis and comment. Subacute veno-occlusive disease with recurrent episodes of ascites, and good clinical recovery, with persisting hepatomegaly. It is of interest to note that the histological appearances in four liver biopsies showed the fibrosis to be progressing continuously during both clinical cure and relapse.

Case 8. P. J. was the five-year-old sister of a boy aged three years, who had been admitted to hospital with acute veno-occlusive disease one week earlier. She had a routine examination in the out-patient department in May 1955. She was completely free from symptoms at the time of examination, and had no previous history of any related illness. The only abnormal finding on physical examination was a liver enlarged almost to the umbilicus. Routine investigations on admission gave normal results, and the liver function tests showed only moderate impairment. She was discharged after four weeks' observation, still free from symptoms, but with persisting hepatomegaly. She has remained clinically well during 15 months' observation as an out-patient, and the liver, which has been gradually reduced in size, is now impalpable.

Histology. Liver biopsy on admission (S/55/689) showed a typical picture of mild veno-occlusive disease. A second biopsy was not obtained.

Diagnosis. Subacute veno-occlusive disease, with symptomless hepatomegaly which has gradually settled in 15 months.

C. *Chronic Veno-occlusive Disease*

The chronic stage is characterized by a cirrhosis which, if the patient has not been seen before, may be clinically indistinguishable from other forms of cirrhosis. It frequently progresses more rapidly than cirrhosis from other causes. In one case a marked cirrhosis was found in biopsy specimens three months after the initial biopsy, which showed venous occlusions, but no fibrosis. An interesting feature of the chronic cases is the frequency with which a continuous venous hum (Cruveilhier-Baumgarten syndrome) is audible on the abdominal or lower thoracic wall. It was heard in six out of 14 patients with chronic veno-occlusive disease, a proportion much higher than we think occurs in cirrhosis

from other causes. It is probably an indication both of the degree of venous obstruction and of the capacity at this age to form an extensive anastomotic circulation.

Case 9. S. B., a poorly nourished nine-year-old boy, was admitted to hospital with a history of repeated haematemeses during the previous two years. For the past three years he had lived in an orphans' home, and a previous clinical or dietary history could not be obtained. There was hard, irregular hepatomegaly and splenomegaly (Plate 28, Fig. 10), and aneurysmal dilated veins were visible on the abdominal wall. A continuous venous hum was audible in the area indicated in Fig. 10. There was no jaundice or ascites. Laboratory investigations gave normal results, apart from the liver function tests. Blood transfusion was required immediately on admission, and had to be repeated at intervals for the following eight weeks because of recurrent haematemeses. Ligature of the splenic artery was carried out when he had been 10 weeks in hospital, in an attempt to prevent further bleeding from the oesophageal varices, which were seen on oesophagoscopy. The haematemeses, however, continued unchecked, and the patient died 78 days after admission.

Liver biopsy and post-mortem findings. Liver biopsy (S/52/286, S/53/76) and post-mortem examination (P.M. 60) showed a finely granular cirrhosis, with collateral vessels as described in Case 5. Histopathologically there was a marked non-portal cirrhosis.

Case 10. P. A., a 13-year-old boy, was admitted to hospital after a haematemesis in July 1954. His abdomen had been 'distended' for varying periods since childhood, but he had never been admitted to hospital, and during the last few years repeated epistaxes and occasional haematemeses had occurred. No further details of his history could be obtained. His nutritional state was poor, and there was oedema of the legs and some ascites. The liver and spleen were both very hard and irregular, and both were enlarged to within 2 cm. of the umbilicus. There was visible distension of the veins on the abdominal wall, but no jaundice. Impaired liver function was again the only significant laboratory finding. Repeated blood transfusions were necessary in hospital, but the patient gradually lapsed into coma, and died 17 days after admission.

Post-mortem findings (P.M. 358). The height of the body was 138 cm., and the weight 23 kg. The liver weighed 830 gm., and showed a uniformly and finely nodular surface. There were oesophageal varices and other collateral vessels, as in Case 9. Histological examination again showed a marked non-portal cirrhosis, with long-standing occlusions of branches of the hepatic veins.

Diagnosis. Chronic veno-occlusive disease, with haematemeses and death in hepatic failure.

Diagnosis in Veno-occlusive Disease

In the acute phase the diagnosis is usually made from the history, the characteristic clinical picture, and the liver biopsy findings. In the subacute and chronic stages the diagnosis may be more difficult, but is again usually easily confirmed by liver biopsy. When jaundice is considerable, infectious hepatitis, leptospirosis, and other causes of hepato-cellular damage must be considered. In all these conditions, however, ascites is unusual. Occasionally the chronic stage is seen for the first time in an acute exacerbation, and distinction from primary or secondary carcinoma of the liver may be difficult. Sometimes the cirrhosis is so gross in the chronic stage that liver biopsy is of

TABLE I

Clinical Summary, Liver Function Tests, and Liver Biopsy Findings in Cases Reported in Text

V.O.D. = veno-occlusive disease

Case number	Clinical type (on admission)	Time of test	Liver function tests: Bilirubin: 1 min. (mg./100 ml.)	Bilirubin: total (mg./100 ml.)	Thymol turbidity (units)	Cholinesterase (units)	Total protein (mg./100 ml.)	Albumin (gm./100 ml.)	Globulin (mg./100 ml.)	Liver biopsy or post-mortem findings	Result
1	Acute	On admission	0·1	0·7	2·3	0·3	5·0	2·5	2·5	Acute V.O.D.	Full recovery
		After 4½ weeks (clinical recovery)	0·2	0·7	2·8	0·8	7·8	4·1	3·7	Normal	
2	Acute	On admission	..	1·0	3·4	0·3	5·3	3·5	1·8	Acute V.O.D.	
		After 4 weeks (improved)	0·1	0·8	1·6	0·47	7·0	4·6	2·4	Acute V.O.D.	Full recovery
		After 8 weeks (recovered)	..	0·6	2·0	0·65	8·1	4·5	3·6	Normal	
3	Acute	No symptoms (routine)	0·1	0·5	2·8	0·61	8·5	4·3	4·2	..	
		Onset of illness (admission)	1·06	2·0	1·6	0·36	5·8	2·9	2·9	Acute V.O.D.	Full recovery
		After 4 weeks (very ill)	2·6	4·0	2·1	0·13	5·6	2·5	3·1	..	
		After 8 weeks (recovery)	1·2	2·4	2·9	0·75	7·7	4·2	3·5	Normal	
4	Acute	On admission (very ill)	2·4	4·2	2·8	0·14	5·8	2·4	3·4	Severe acute V.O.D. (post-mortem)	Death in hepatic failure 15 days after admission
5	Acute	On first admission	0·3	2·0	1·6	0·21	4·8	2·7	2·1	Acute V.O.D.	
		After 8 weeks (very ill)	0·4	2·0	5·0	0·09	4·9	1·9	3·0	V.O.D. with centrilobular fibrosis	Steady progression to cirrhosis, and death from haematemesis 15 months from acute onset
		After 3 months (on discharge)	..	..	3·0	0·40	6·9	2·8	4·1	Marked centrilobular fibrosis	
		Second admission (6-months assessment)	..	..	1·4	0·58	6·3	4·3	2·0	Non-portal cirrhosis	
		Third admission (haematemesis)	0·4	1·6	3·3	0·27	6·8	2·8	4·0	Non-portal cirrhosis (post-mortem)	
6	Acute	On admission	2·2	6·0	2·7	0·39	5·1	2·2	2·9	Acute V.O.D. (post-mortem)	Death in hepatic failure 10 days after admission
7	Subacute	First admission	..	..	2·8	0·31	6·1	3·0	3·1	V.O.D. (typical but not severe)	Clinical improvement, but with progressive hepatic fibrosis
		After 6 weeks (on discharge)	0·1	0·6	3·8	0·47	7·6	4·5	3·1	Progressive fibrosis	
		Second admission	0·2	0·9	4·2	0·50	7·5	4·0	3·5	Further fibrosis	
		After 3 weeks (on discharge)	..	0·8	4·3	0·46	7·3	3·6	3·7	Further fibrosis	
8	Subacute	On admission (symptomless hepatomegaly)	0·1	1·1	1·0	0·4	7·7	2·4	5·3	V.O.D. (typical but not severe) (Second biopsy not obtained)	Clinical improvement
9	Chronic	On admission	..	0·8	4·0	0·37	8·4	3·9	4·5	Liver biopsy and post-mortem findings: chronic V.O.D. with cirrhosis	Death from haematemesis 11 weeks after admission
10	Chronic	On admission	..	..	2·4	0·35	7·8	3·0	4·8	Liver biopsy and post-mortem findings: chronic V.O.D. with cirrhosis	Death from haematemesis 17 days after admission

little assistance in diagnosis. Veno-occlusive disease is suspected, however, when cirrhosis occurs at an unusually early age, and frequently a history of an abrupt onset of 'swell-belly' some years earlier is obtained.

Patients Investigated and Methods

A clinical analysis has been made of 84 Jamaican patients, 45 male and 39 female, suffering from veno-occlusive disease. Sixty-one were admitted to the University College Hospital in the last four years, and 23 to the Kingston Public Hospital (Dr. Rhodes) in the preceding 18 months. Sixty-four cases were classified as acute when first seen, six as subacute, and 14 as chronic. The initial classification in all cases was based on the clinical picture and the liver biopsy, and sometimes on post-mortem findings. The ages of the patients on admission ranged from six months to 53 years. The overall average stay in hospital was 93 days. In the acute cases with complete recovery the average hospital time was significantly lower, being 55 days. Patients were followed up after discharge in the out-patient departments. House-to-house follow-up was necessary in a number of cases in which patients failed to attend. Seventy-three have been followed up for periods of from six months to five years.

Liver biopsy was performed on all patients (except those very ill) on admission, and at varying intervals while in hospital. One hundred and seventy-three biopsies were done. A number of patients were readmitted, while free from symptoms, for follow-up biopsies, if progression to hepatic fibrosis was suspected. Liver biopsy was done with the Vim-Silverman needle, using the modified technique described by Hoffbauer (1947). The transpleural approach was used in most cases, but in patients with large pleural effusions the subcostal route was considered safer. No mishaps occurred from these procedures. A shock-like state occurred in two patients after biopsy, and lasted for two to three hours. It was attributed to pleural shock, there being no clinical evidence of bleeding at the time or subsequently. The belief that the liver biopsy in these patients is representative of generalized changes throughout the liver has been adequately confirmed by comparison with post-mortem material. A full post-mortem examination was made in 21 out of 26 fatal cases. The liver biopsy and post-mortem findings have been described in previous papers (Bras, Jelliffe, and Stuart, 1954*a*, *b*; Bras and Watler, 1955).

Liver function tests were also done in all cases on admission, and at intervals throughout the stay in hospital and in the out-patient departments. The one-minute and total bilirubin was measured by the method of Ducci and Watson (1945). Thymol turbidity was estimated by using the thymol solution of pH 7·55 of Mateer, Baltz, Steele, Brouwer, and Colvert (1947), and serum-cholinesterase by a modification of Michael's electrometric method (Reinhold, Tourigny, and Yonan, 1953). The serum-proteins were estimated by the biuret method, and alkaline phosphatase by the method recommended by King (1951). The following additional clinical investigations were done in all cases: haemoglobin, white-cell count, and differential count; erythrocyte sedimentation

rate; tests for sickling; bleeding and clotting times (and prothrombin estimations if clotting was prolonged or the serum-bilirubin level unusually elevated); serological tests for syphilis; urine analysis for albumin, sugar, acetone, bilirubin, and urobilin; and stool examinations for cysts, ova, and protozoa. Chest X-rays and electrolyte estimations were done in most cases. Quantitative estimations of glycogen, fat, and water-content were made in a number of liver biopsy specimens. A report on these findings is in preparation.

TABLE II

Follow-up Data and Present Clinical Status in 64 cases of Acute Veno-occlusive Disease

Clinical status	*Duration of follow-up (years)*					*Total*	%
	½–1	*1–2*	*2–3*	*3–4*	*Over 4*		
Dead	..	..	..	..	..	17	27
Untraced	..	..	..	..	..	6	9
Chronic cirrhosis	0	2	1	0	4	7	11
Subacute	2	1	..	..	..	3	5
Normal	5	7	4	6	9	31	48
Total	7	10	5	6	13	64	..

The clinical course of individual patients after admission, and the response to treatment, are variable and often unpredictable. For this reason it was thought worth while to attempt to find some clinical and biochemical criteria which, on the patient's admission, might be of assistance in predicting the course and prognosis of the disease. A detailed analysis has therefore been made of the common clinical and biochemical features found immediately after admission in the 64 patients admitted in the acute stage; and the findings in the patients who recovered, and in those who died or progressed to fibrosis, have been compared (Fig. 2 and Table III). The present clinical status of these 64 patients, and the duration of follow-up, are shown in Table II. Table IV shows the mortality rates and causes of death in each of the three clinical groups.

Results

Age incidence and mortality rates. The overall age incidence and mortality rates in the eighty-four cases studied are shown in Fig. 2. The highest incidence occurs between one and three years, 33 patients (39 per cent.) being in this age-group. There were 22 patients (26 per cent.) in the three-to-six-year group, so that these two groups accounted for 65 per cent. of the total. Although the disease is relatively uncommon in adults compared with children, they constitute 13 (16 per cent.) of the 84 patients. It is also shown that, although veno-occlusive disease is relatively uncommon at the two extremes—early infancy and adult life—the mortality rate is highest in these two groups, being 60 per cent. and 54 per cent. respectively of the patients in these categories.

The clinical and laboratory findings are summarized in Fig. 3 and Table III. This analysis was mainly concerned with the 64 patients admitted in the acute stage of the disease. In patients seen for the first time in the subacute or chronic stages it was thought that there were too many undetermined factors for

detailed analysis to be useful in assessing prognosis. Hepatomegaly and ascites of some degree are almost invariable in acute cases. In 48 of the 64 patients the ascites was sufficiently large to require paracentesis shortly after admission, as

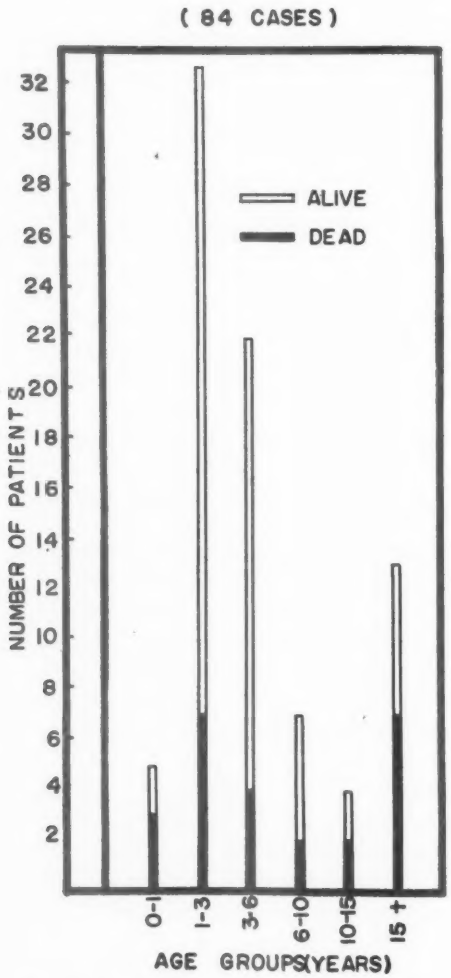

FIG. 2. Age incidence and mortality rates in veno-occlusive disease.

many as 12 paracenteses being required subsequently in some cases. In 38 patients the enlargement of the liver reached more than half-way from the costal margin to the umbilicus. Reference to the umbilicus was chosen in order to emphasize the considerable hepatomegaly that is usual in these patients. The other findings in descending order of frequency were: oedema, usually of the lower

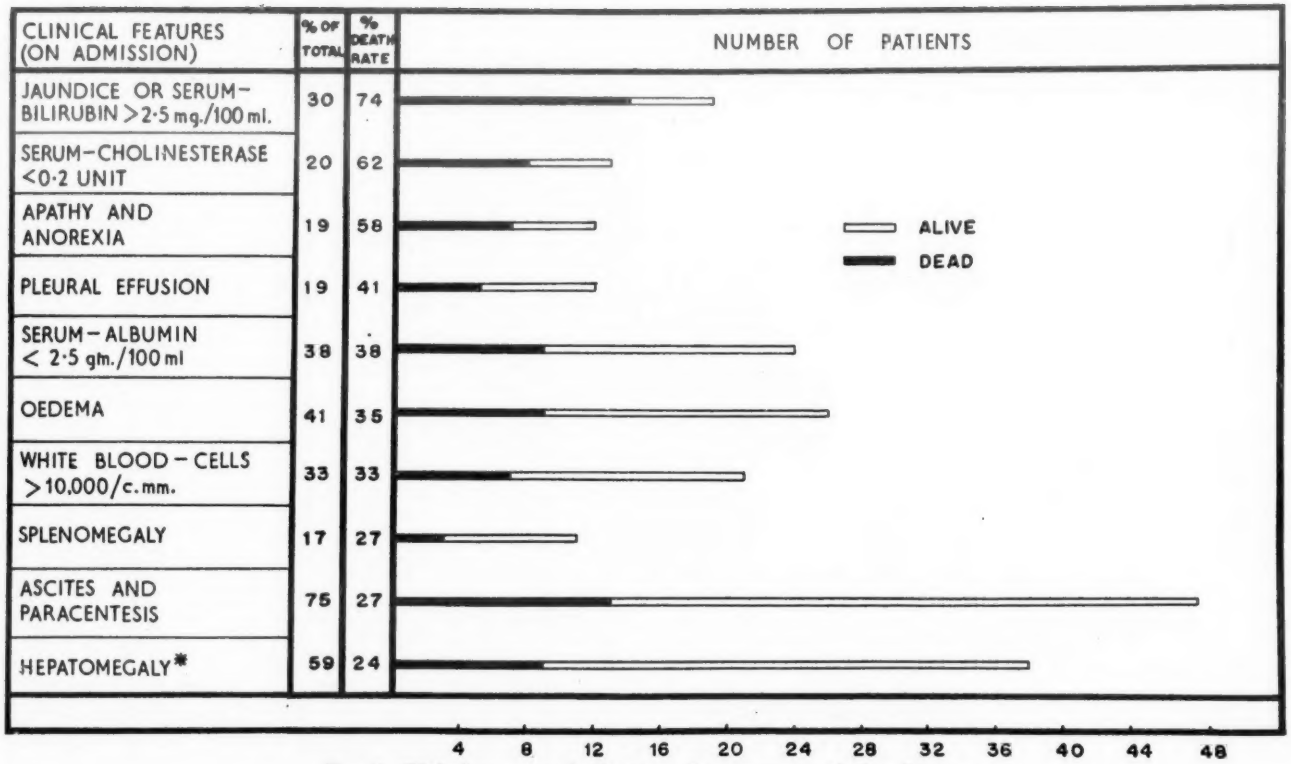

FIG. 3. Clinical summary in 64 cases of acute veno-occlusive disease.

* Hepatomegaly = enlargement to half-way from costal margin to umbilicus, or more.

limbs, sometimes generalized; serum-albumin values of less than 2·5 gm. per 100 ml.; a white-cell count more than 10,000 per c.mm.; clinical jaundice, or serum-bilirubin more than 2·5 mg. per 100 ml.; serum-cholinesterase less than 0·2 unit (Michel); apathy and anorexia; pleural effusion; and splenomegaly. The

TABLE III

Average Serum-Cholinesterase and Albumin Levels in Acute Veno-occlusive Disease

Category of patients	*Time of test*	*Cholinesterase (units)*			*Albumin (gm./100 ml.)*		
		Average	*Range*	*Standard deviation*	*Average*	*Range*	*Standard deviation*
Dead or now with cirrhosis (24)	Admission	0·2	0·08–0·3	0·08	2·3	1·7–2·9	0·3
Recovered (31)	Admission	0·31	0·15–0·7	0·13	2·8	1·7–4·2	0·54
	Discharge	0·64	0·32–0·91	0·15	3·7	2·6–4·6	0·43
Normal Jamaican adults (Garrow, 1954)	..	0·56	0·36–0·78	..	3·9	2·5–5·5	..

mortality rates associated with each of these findings are also shown in Fig. 3. It is interesting to note that the mortality rates associated with signs of parenchymal liver damage were relatively high, being 74 per cent. with clinical jaundice or high levels of serum-bilirubin, 62 per cent. with diminished serum-cholinesterase, and 58 per cent. when apathy and anorexia were considerable. The figures were much lower with the clinical features attributable solely to hepatic venous obstruction: with marked hepatomegaly 24 per cent., with ascites requiring paracentesis 27 per cent., and with splenomegaly 27 per cent.

Liver function tests showed some derangement in all cases, however mild (Table I), but the most consistent and significant changes were found in the serum-cholinesterase and serum-albumin levels (Table III). The average serum-cholinesterase and serum-albumin levels on admission, in the 31 patients who recovered, were 0·31 unit and 2·8 gm. per 100 ml. respectively. Corresponding figures in the 24 patients who either died (17) or progressed to fibrosis (seven) were 0·2 unit and 2·3 gm. per 100 ml. The range and standard deviation of these estimations in the two categories are shown in Table III. We have used a 't' test to compare the mean cholinesterase and albumin levels in these two groups, and there is a statistically significant indication that they are not from the same 'population' (cholinesterase: $t = 2{\cdot}67$, $0{\cdot}02 > P > 0{\cdot}01$; albumin: $t = 2{\cdot}82$, $0{\cdot}01 > P$). It is therefore reasonable to assume that these tests on admission provide a good guide in assessing prognosis. The overlap of the ranges, however, still makes it difficult to predict accurately the outcome in any individual patient.

Clinical follow-up and mortality. The present clinical status of the 64 patients admitted with acute veno-occlusive disease is shown in Table II. Seventeen (27 per cent.) are dead, and six (9 per cent.) failed to attend. At the time of discharge these patients had shown complete clinical recovery, but no repetition

of liver biopsy had been obtained. Seven patients (11 per cent.) have developed chronic cirrhosis, diagnosed clinically and histologically, and three are in the subacute phase, with symptomless hepatomegaly or hepato-splenomegaly, and occasionally recurring ascites. Thirty-one (48 per cent.) show complete clinical, biochemical, and histological recovery.

The causes and number of deaths in patients admitted in the three main clinical stages are shown in Table IV. Of the 17 deaths in 64 acute cases, 12

TABLE IV

Mortality Rates and Causes of Death in Veno-occlusive Disease

Clinical type	*Number of patients*	*Deaths*	*Death rate %*	*Cause of death*		*% Cause of death*	*Average duration of illness*
Acute	64	17	27	Hepatic failure and cholaemia	12	71	25 days
				Haematemesis	5	29	29 months (9 months to 5 years)
Subacute	6	1	17	Hepatic failure	1	..	Unknown
Chronic	14	8	57	Haematemesis	6	75	Unknown
				Hepatic failure	1	12·5	Unknown
				Accidental	1	12·5	Unknown

were due to hepatic failure (two with an associated respiratory infection) within an average of 25 days of admission. Five patients in this group died of haematemeses, having progressed to the chronic stage in an average period of 29 months (nine months to five years). Of the six patients admitted in the subacute stage, one died of hepatic failure. Six out of 14 patients admitted in the chronic stage died of haematemeses, one in hepatic failure, and one in a road accident after discharge. The total number of deaths from haematemeses in all groups was 11 (42 per cent. of 26 fatal cases), five patients having progressed from the acute stage to cirrhosis and terminal haematemeses while under observation. Hepatic failure accounted for a total of 14 deaths (54 per cent. of 26 fatal cases), and usually occurred early in the disease (Table IV). The overall mortality rate from these figures is 30 per cent., and further deaths can be anticipated among patients who are untraced or now in the cirrhotic stage.

Pathology. When the first two cases of this condition were seen they were diagnosed on the liver biopsy findings as Chiari's syndrome. It soon became evident, however, that we were dealing with a condition which was unlike most reported cases of this syndrome; the lesions seemed to be most marked in the *smaller* branches of the hepatic veins, and obvious thrombosis could not be demonstrated. The histological picture, however, was very similar to the condition described by Rössle (1933) and Teilum (1949) as endophlebitis obliterans hepatica. The lesion is invariably confined to the central and the next larger branches of the hepatic veins, leaving the main branches entirely free; and it affects these vessels uniformly throughout the liver. This is well demonstrated in Plate 30, Figs. 12 and 13, which are X-ray pictures of a liver, in a fatal case of acute veno-occlusive disease, after post-mortem injection of the hepatic vein with barium. In comparison, Plate 31 (Figs. 14 and 15) shows the results of the same procedure in a normal liver. It is clear that in the diseased liver the

larger branches were filled with barium, whereas the smaller branches were not penetrated. Histopathologically and histochemically the acute lesion appears to be a swelling of the subintimal tissues due to oedema (Plate 29, Fig. 11). We have been unable to demonstrate that constituents of the blood or plasma are responsible for this swelling, although it could conceivably be a mural deposition of such constituents, becoming overgrown later by endothelium, and thus producing a so-called 'Duguid lesion'. In later stages the oedema becomes collagenized, but, as remarked in the case histories, a remarkable degree of regression is possible; and our observations indicate that this acute swelling can come and go in a very short period. We have been unable to demonstrate any direct damage of the parenchymal cells of the liver preceding the vascular changes, and all the lesions noted could be traced back to the veno-occlusion. The immediate sequelae are congestion of the sinusoids and a pressure-degeneration of the hepatic cell-cords in the centrilobular areas, extending sometimes to the portal areas if the occlusion is severe. The centrilobular liver-cells may undergo a varying degree of degeneration, from fatty change to complete necrosis. If this necrosis appears rapidly and is extensive, there is an associated clinical picture of hepatic failure. It appears, therefore, that in acute veno-occlusive disease the prognosis is immediately linked with the degree of centrilobular destruction of the liver-cells, the cases that come to autopsy showing lesions similar to, but more extensive than those found in patients who recover.

It is also clear that in the acute stage the reticulin framework of the liver is not damaged, and when the venous occlusion subsides, and the sinusoids cease to be congested, regeneration of liver-cells, with growth into the scaffolding of the reticulin framework, may be a rapid and complete process, leaving no residual changes. When the venous occlusion is repeated, or does not subside completely, there is a residual collapse of the centrilobular reticulin framework, which is soon followed by proliferation of fibrous tissue—apparently at first with the production of argyrophil fibres, which later become collagenized. In this way a *non-portal* fibrosis develops. This process of scarring causes an approximation of the hepatic vein and the portal triad, and also an approximation of several neighbouring portal triads. When the process is repeated, which the case histories indicate is a not infrequent occurrence, there may be gradual involvement of more and more of the liver lobule, and in some circumstances the scar may come to include former portal triads. As the fibrosis advances, collateral vessels short-circuit the portal vein and the non-occluded part of the hepatic venous tree, producing relative or absolute ischaemia of other liver-cells, again with necrosis and scarring as the sequelae; and so the fibrosis, once initiated, becomes progressive and self-aggravating. The end-result is therefore a true cirrhosis, with distortion of the lobular architecture of the liver and the development of collateral circulation and regeneration nodules, the surface usually presenting a finely granular to nodular appearance. Even in the most advanced cases, however, the original non-portal distribution of the fibrosis is recognizable; and in all the cases we have examined so far there were a large number of portal triads which remained completely unaffected.

Discussion

Age incidence. The relatively low incidence of veno-occlusive disease in children under one year is probably due to the fact that breast-feeding is normally continued for about nine months, and sometimes longer. In the succeeding years of childhood it appears that the liver is peculiarly susceptible to nutritional or toxic damage. It is in the years after weaning that the syndrome of protein malnutrition, kwashiorkor, is commonest; and Rhodes (1954) has produced evidence that, whatever the apparent nutritional status of the patient, veno-occlusive disease is invariably associated with lack of protein in some degree. The precise role of malnutrition in veno-occlusive disease is at present undetermined, and, as far as we know, the lesion has not been produced experimentally by dietary methods alone. We believe that malnutrition plays an important but subsidiary part, most likely as a contributory cause, and in affecting the prognosis. In children under two years of age with veno-occlusive disease the fatty changes in the liver, found in kwashiorkor, are also invariably present; and Waterlow (1948) has already stressed the high mortality of fatty liver disease in West Indian infants. It therefore seems likely that the association of veno-occlusive disease and fatty liver disease is responsible for the very high mortality rate found in the under-one-year age-group (Fig. 2).

There is convincing evidence, detailed later, that veno-occlusive disease is a form of toxic liver damage, and probably produced by local plant toxins. Another instance of toxic liver injury, also occurring particularly in the age-group one to six years in which veno-occlusive disease is commonest, is seen in the 'vomiting sickness of Jamaica'. The main clinical features of this condition, which also invariably occurs in relatively under-nourished subjects, have been recently reviewed (Stuart, Jelliffe, and Hill, 1955), and the probable role of the immature ackee (*Blighia sapida*), a commonly used and popular food when ripe, has been shown by Hassall, Reyle, and Feng (1954). It therefore seems possible that in such children ingested toxins can more easily damage a malnourished than a normal liver. It has been shown experimentally that nutritional deficiency may predispose the liver to damage from toxins of a chemical or bacterial nature (Miller and Whipple, 1940; Smith, 1941). The high incidence of toxic liver damage at these ages, and the very high mortality rates in infants, may also be due to their much lower body-weight, increasing the relative toxicity of an ingested poison.

There is a rather low incidence, but much higher mortality, in adults compared with children (Fig. 2). Whereas 74 per cent. of cases occurred between the ages of one and 10 years, and only 16 per cent. in patients over 15 years, the corresponding mortality rates were 20 per cent. and 54 per cent. respectively. It has been shown in other forms of liver injury (Weil's disease (Davidson, 1951); infectious hepatitis (Stokes, 1951)) that the prognosis is decidedly influenced by age, being better in children and adolescents than in adults. A comparable finding in injury due to veno-occlusive disease is therefore not surprising.

Clinical features. Previous reports on hepatic venous occlusion (Chiari, 1899;

Rao, 1935–6; Teilum, 1949) have been based on post-mortem examination in fatal cases. By serial liver biopsies in the present series of cases it has been possible to demonstrate (1) the reversibility of the hepatic venous occlusions in the early stages of the disease, and how closely it is related to the disappearance of ascites and hepatomegaly, and to changes shown by the liver function tests (Table I); (2) the progression to cirrhosis in some cases; and (3) the rapidity with which both these processes may occur (see Cases 1 and 5). The abrupt onset and frequently rapid disappearance of a gross hepatomegaly and voluminous ascites certainly provide the most striking clinical features in the acute stage of the disease. When cirrhosis is present, either in chronic veno-occlusive disease or from other causes, it is likely that one or more of several factors—circulatory and hydrostatic, osmotic, nutritional, renal, and endocrine—may operate together in the production of ascites. In acute veno-occlusive disease, however, it would appear that both hepatomegaly and ascites are the immediate mechanical results of hepatic congestion produced by occlusion of the hepatic veins. There is no constant correlation in acute veno-occlusive disease between the blood colloidal pressure and the rate and volume of accumulation of ascitic fluid. A tense ascites frequently occurs with serum-albumin levels above 3 gm., and sometimes above 4 gm., per 100 ml. Recent experiments have shown the importance of hepatic venous congestion in the production of ascites (Volwiler, 1951; Schilling, McCoord, Clausen, Troup, and McKee, 1952); and obstruction of the inferior vena cava above the diaphragm has become the standard procedure in producing ascites in experimental animals. The high protein-content of the ascitic fluid (usually 2 to 2·5 gm. per 100 ml.), and the demonstration of a marked increase in the size, and perhaps the number, of the hepatic lymphatics in acute veno-occlusive disease, are also in keeping with the findings in experimental ascites in animals (Volwiler, 1951), and suggest that in man also an augmented lymph-flow in the liver may be the main source of ascitic fluid formation when the hepatic venous outflow is obstructed. The rapid appearance of hepatomegaly and ascites in acute veno-occlusive disease also parallels very closely the events in animal experiments, and, in the early stages of the disease at any rate, they sometimes disappear as promptly as they do in the 'ascitic' dog preparation with release of venacaval constriction.

The disappearance of hepatomegaly and of ascites marks focal points in the progress of the disease, and the longer they persist the worse the prognosis. Prolonged hepatic congestion is recognized as an important factor in the production of permanent structural changes in the liver (Himsworth, 1950), and a progressive fibrosis was found to occur more commonly in cases in which it persisted longest. It also appears that once the fibrosis has passed a certain stage, and long after the specific action of the pathogenic agent has ceased, the circulatory derangements are such as to ensure its automatic and inevitable further development. It is this circumstance that accounts in large part for the relentless progress and ultimately hopeless prognosis in the later stages of veno-occlusive disease. There is still some doubt as to whether the fatty liver changes of kwashiorkor in Jamaica and other tropical countries progresses

eventually to fibrosis; and, as far as we know, no account has yet been published showing in man all the stages of transition from fatty infiltration to fibrosis, such as can be easily demonstrated in the rat. In veno-occlusive disease, however, it has now been established beyond reasonable doubt that there is frequently a steady sequence from the acute lesion to a progressive and irreversible cirrhosis.

TABLE V

Clinical Comparison of Infectious Hepatitis and Acute Veno-occlusive Disease

	Infectious hepatitis (after Sherlock, 1955)	*Acute V.O.D.*
Jaundice	Common, often severe	Infrequent, seldom severe except terminally
Apathy and malaise	Usually severe: early	Uncommon, mild, and usually late
Anorexia and vomiting	Often very severe	Mild
Hepatomegaly	+	+++
Hepatic tenderness	Marked	Slight
Ascites	Very uncommon	Usually gross
Progression to cirrhosis	Variable, but uncommon	Common
Urine	Dark: urobilinogen+, bilirubin+	Usually normal
Stools	Clay-coloured	Usually normal
White-cell count	Often leucopenia	Usually normal, sometimes leucocytosis
Fever over 100·5° F.	Common	Rare, except with concurrent infection
Mortality	Variable, but usually low	High
Initial histological findings in liver	Hepato-cellular necrosis	Hepatic venous occlusion

A comparable condition occurs clinically and histologically in Chiari's syndrome of obliterating endophlebitis of the hepatic veins (Chiari, 1899), in liver cirrhosis in Egyptian children (Hashem, 1939), with senecio poisoning in South Africa (Selzer and Parker, 1951), and in cirrhosis in infants in India (Rao, 1935–6; Chaudhuri, 1944; Misra, 1950). The Indian disease, which occurs particularly in Madras and Bengal, has many points of close similarity with Jamaican veno-occlusive disease, presenting the abrupt onset of hepatomegaly and ascites, and often terminating in the acute phase with cholaemia or progressing to fibrosis. It differs, however, in that (1) it usually occurs in middle-class Brahmin Hindu families, the poorer classes appearing relatively immune, (2) the onset is usually earlier, with an earlier onset of jaundice, and (3) it runs a more rapidly fatal course, often terminating 'malignantly' in cholaemia within a few weeks, or progressing to a fatal cirrhosis in one to two years. A similar rapidly fatal course does occur in some Jamaican patients (Case 6), but a slower progress is more usual.

It is interesting to compare acute veno-occlusive disease, in which the primary lesion is vascular obstruction, with infectious hepatitis, in which the initial damage is hepato-cellular necrosis. The contrasting clinical features of these two types of liver injury are shown in Table V. The hepatomegaly and ascites

which give veno-occlusive disease its peculiarly distinctive clinical characteristics are almost invariably present, and appear early in the disease, whereas jaundice, apathy, and anorexia, the characteristic findings in infectious hepatitis, occur infrequently, and are conspicuous only in severe cases. The relatively high mortality associated with the clinical manifestations of hepato-cellular damage in veno-occlusive disease is shown in Fig. 3. It can be concluded (1) that hepato-cellular damage, when present in this disease, is always secondary, and varies directly with the degree of venous occlusion, and (2) that parenchymal liver damage, occurring with the lesions of veno-occlusive disease, has a worse prognosis than when one or the other disorder exists alone.

Pleural effusions are not uncommonly found in association with ascites. The relatively high incidence of large effusions in the present series was probably due to the considerable ascites that often existed, and large effusions were not seen in patients without, or with only slight, ascites. They may be due to the leakage of fluid through the diaphragmatic lymphatics into the pleural cavity. Such a flow can be shown by injection of a foreign dye into the ascites and its subsequent demonstration in the pleural cavity (Sherlock, 1955). A relatively low serum-albumin level, due both to impaired liver function and to loss in the ascitic fluid, may have contributed in part to their formation. Pulmonary tuberculosis was found in only one patient in this series (an adult without pleural effusion), and was not thought to be related to his illness. Oedema, when present, was confined to the legs, and usually disappeared with the ascites. In three cases, in which there was generalized oedema, the low serum-albumin level (1·8, 2·0, and 1·6 gm. per 100 ml.) was probably responsible. As in other types of liver disease, a decreased destruction of antidiuretic hormone by the diseased liver (Gopalan, 1955), may have played a part. There was no evidence clinically, electrocardiographically, or *post mortem*, of any associated heart disease in these patients.

Liver function tests. Details of the 10 cases reported in the text are given in Table I. The average serum-cholinesterase and serum-albumin levels on admission and on discharge in 31 patients who recovered, and on admission in 24 patients who have either died or progressed to cirrhosis, are shown in Table III. None of the other tests of liver function employed appeared to mirror the changing state of the hepatic parenchyma as sensitively as the serum-albumin and, more especially, the serum-cholinesterase. There is much evidence to confirm the belief that the serum-cholinesterase molecule is synthesized in the liver (Kunkel and Ward, 1947; Sawyer and Everett, 1947; Wescoe, Hunt, Riker, and Litt, 1947), and probably in parallel with the albumin molecule. Serial studies of serum-cholinesterase in both acute and chronic disease of the liver have shown that changes in its concentration closely reflect changes in hepatocellular function (Vorhaus and Kark, 1953). Normal values have been established for Jamaican adults—0·36 to 0·78 unit (Garrow, 1954)—but not for children, and the wide range of normal values described elsewhere sometimes makes interpretation of single measurements difficult. Patients in whom the lowest initial values were found on admission have suffered a relatively high

mortality (Table III and Fig. 3), while those who have recovered showed a significantly higher initial reading; but the widely overlapping ranges of albumin and cholinesterase in these two groups show that the findings can be no more than useful guides in assessing the prognosis of any given patient on admission. It is recognized that low serum-cholinesterase levels may be found in a number of other conditions: malnutrition and chronic debilitating diseases (Faber, 1943;

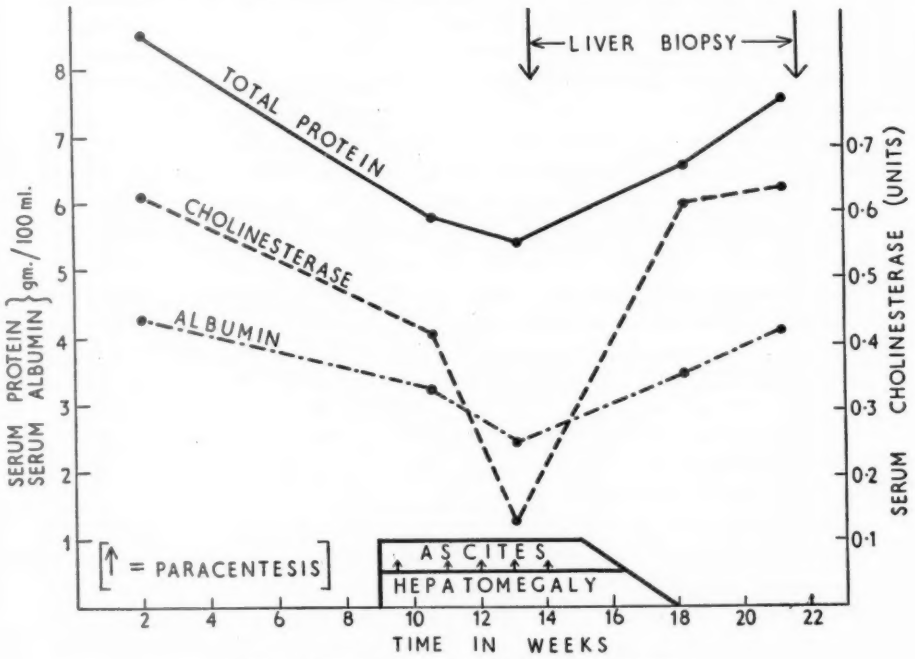

FIG. 4. Case 3. Clinical and laboratory features.
By courtesy of the *British Medical Journal*.

Vorhaus and Kark, 1953), acute infectious diseases (Hall and Lucas, 1937; Dikshit and Mahal, 1937–8), and various types of anaemia (Sabine, 1940; Sawitsky, Rowen, and Meyer, 1949). This fact increases still further the difficulty of interpreting single readings. We have found serial measurements of this enzyme, however, to be useful in evaluating the condition of patients suffering from this disease, and particularly in following its course. Parallel changes occur in serum-albumin levels, but are rather less pronounced (Table I). The characteristic findings in a patient who recovered (Case 3) are shown in Fig. 4.

Aetiology. Theories of the aetiology of this syndrome have been discussed in previous papers (Rhodes, 1954; Bras, Jelliffe, and Stuart, 1954*a*, *b*; Jelliffe, Bras, and Stuart, 1954), and the probable role of toxins of plant or vegetable origin considered. Further evidence has been obtained incriminating some of the wide variety of 'bush teas'—infusions of herbs, seeds, and roots—used in Jamaica both medicinally and for food. Asprey and Thornton (1954) have

listed more than 200 plants so used. It was thought that, if this hypothesis of aetiology were correct, the condition should be found in Jamaican cattle or other herbivores. The recent finding of the identical histological lesion, and marked ascites, in a Jamaican cow which died of an otherwise unexplained illness, appeared to give further support to the hypothesis (Bras and Berry, 1956). Further circumstantial evidence was obtained by botanical examination of a number of bushes sold in a large Jamaican market (Palmer, 1956). It was found that there is an extensive use, under a variety of local names, of species of two known hepatotoxic plants, *Senecio* and *Crotalaria*, both of which have been shown to produce hepatic lesions identical with veno-occlusive disease.

Senecio. Selzer and Parker (1951) have reported from South Africa a series of cases which began as acute Chiari's syndrome, and were due to eating bread made from inadequately winnowed wheat contaminated by a species of *Senecio* or ragwort. The clinical picture closely resembled the acute cases of veno-occlusive disease reported above, being characterized by the sudden onset of hepatomegaly—often of considerable degree—and ascites. Post-mortem examination in five fatal cases showed extensive occlusion of the hepatic veins. The hepatotoxic effects of the senecio alkaloids retrorsine (Davidson, 1935; Selzer, Parker, and Sapeika, 1951) and longilobine (Henderson, Harris, and Chen, 1951) have also been demonstrated in experimental animals. More recently it was possible, through the courtesy of the Veterinary Department in Weybridge, Surrey, England, to examine material from a cow suffering from *Senecio jacobaea* poisoning, and the histological picture was indistinguishable from that seen in veno-occlusive disease in Jamaica.

Crotalaria retusa. In three cases of veno-occlusive disease recently reported from Barbados, another West Indian island, *Crotalaria retusa* had been given extensively and exclusively as a 'bush tea' for whooping-cough shortly before the onset of the illness (Stuart and Bras, 1956). This finding prompted investigation of a veterinary report from Australia of horses dying of liver disease as a result of consumption of *Crotalaria retusa* (Bull, 1955). We were able to obtain a specimen of liver from one of these animals through the courtesy of Dr. Bull, and a histological picture identical with veno-occlusive disease was again observed.

There is thus an increasing weight of evidence that a number of 'bush teas', particularly those made from *Crotalaria retusa* and species of *Senecio*, may be important aetiological factors in the disease. Working on this hypothesis, the University of Pennsylvania (Dr. Paul Gyorgy) and the Jamaican group have for the past four years undertaken experimental studies to assess the toxicity in animals of several Jamaican 'bush teas'. The results of these studies will be reported elsewhere.

Conclusion

At present it is not possible to do more than define the essential clinical and histological features of veno-occlusive disease. That it is a distinct disease seems certain. There are three points at present not explained. These are (1) the exclusive (initial) involvement of the hepatic venous tree; (2) the precise role of

malnutrition; and (3) the specific aetiological agent or agents. It is certain, however, that it is the liver lesion which dominates the course of the disease, makes it refractory to treatment by ordinary methods, and causes death in a high proportion of cases. As a common cause of hepatic cirrhosis in Jamaica (and the most common in children), as an illness with a high morbidity and high immediate and late mortality, it constitutes an important challenge to medicine in the West Indies; and, in spite of the gaps in our knowledge, the presumption is strong that it can be prevented.

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Summary

A study has been made of 84 Jamaican patients suffering from veno-occlusive disease of the liver, and 73 have been followed up for periods from six months to five years. Clinically the disease is characterized by three overlapping stages. There is an acute stage, characterized by the sudden development of hepatomegaly and ascites, usually in children between one and six years. In the subacute stage there is a persistent, often symptomless, hepatomegaly; while the chronic stage may be almost indistinguishable clinically from cirrhosis of the liver due to other causes.

Serial liver biopsies have been of value in elucidating the pathological processes in the liver in the three stages of the disease, and also in following the clinical course and in assessing the prognosis. The primary lesion in the acute stage is widespread occlusion of the smaller and medium-sized branches of the hepatic veins, with a varying degree of sinusoidal congestion, and pressure-necrosis of the parenchymal cells around the central veins. This is followed in some cases by the development of a non-portal type of cirrhosis, originating around the central veins.

The hepatomegaly and ascites are considered to be the direct mechanical results of obstruction to the hepatic venous outflow.

Forty-eight per cent. of patients showed complete clinical, biochemical, and histological recovery. Nineteen per cent. died early in the disease of hepatic failure. The remainder passed into the chronic stage, either directly or after an interval of apparent clinical recovery; a number continued in the subacute stage for months or years.

The death-rate is highest in infants under one year and in adults. A high mortality is shown to be associated with early clinical or biochemical evidence of marked hepato-cellular damage, or marked pressure-necrosis of the parenchymal cells in liver biopsy specimens. The value of serum-albumin and serum-cholinesterase estimations, both in assessing prognosis initially and later, when serially recorded, in following the course of the disease, is stressed.

The aetiology is unknown; but it does not appear to be primarily or entirely nutritional. The possibility that veno-occlusive disease is produced by the action of plant toxins is considered with special reference to 'bush teas', which are widely used in Jamaica, and the probable role of species of *Senecio* and *Crotalaria retusa* is discussed.

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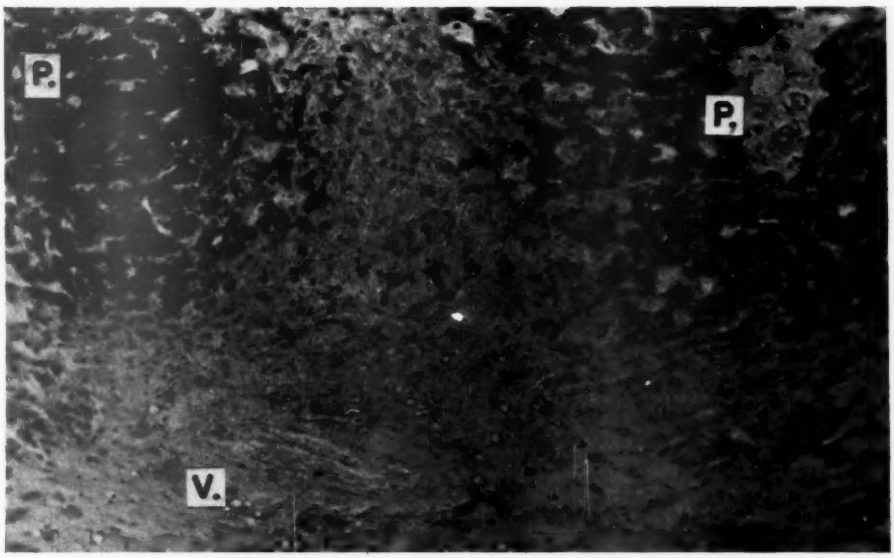

FIG. 5. Case 1. Acute veno-occlusive disease. Histological section of first liver biopsy. Periodic-acid Schiff stain, rendering glycogen dark in the photograph (× 167). Only the periportal areas show glycogen-containing liver-cells

P = portal triad. V = occluded branch of hepatic vein in centrilobular area

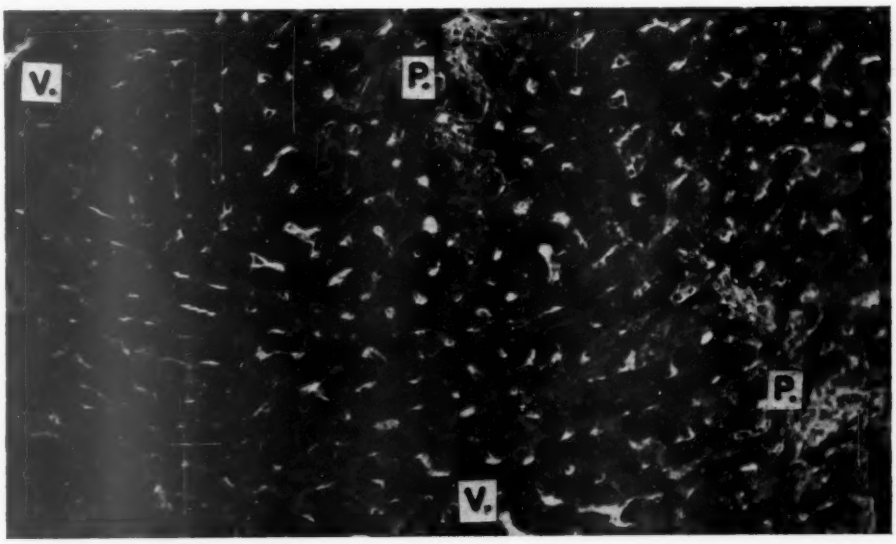

FIG. 6. Case 1. Recovery. Histological section of second liver biopsy, stained as in Fig. 5 (× 167). There is complete regeneration. All liver-cells, including those in the centrilobular areas, contain glycogen, and appear normal

P = portal triad. V = centrilobular areas

FIG. 7

FIG. 8

FIG. 9

FIG. 10

FIG. 7. Acute veno-occlusive disease. Age two years (Case 5). Note tense ascites and hepatomegaly
FIG. 8. Subacute veno-occlusive disease. Age five years (Case 7). Note hepatomegaly and fair state of nutrition
FIG. 9. Late subacute veno-occlusive disease. Age five years. Note hepatomegaly and splenomegaly
FIG. 10. Chronic veno-occlusive disease. Age nine years (Case 9). Note hepatomegaly and splenomegaly, and poor state of nutrition. Circle indicates the site of venous hum

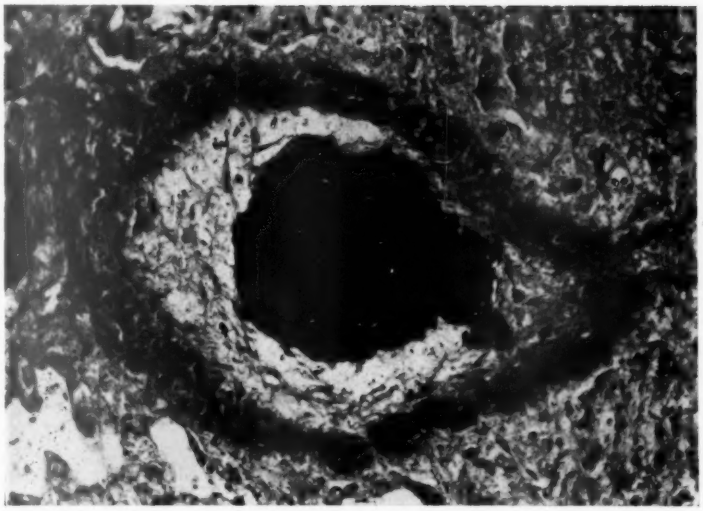

FIG. 11. Histological section of liver from a fatal case of acute veno-occlusive disease. Mallory trichrome stain (×190). The hepatic venous tree was injected *post mortem* with Indian-ink gelatin. The picture shows a hepatic vein with sub-intimal swelling. The narrowed lumen is filled with Indian ink. (P.M. No. 548: Female child aged 3 years)

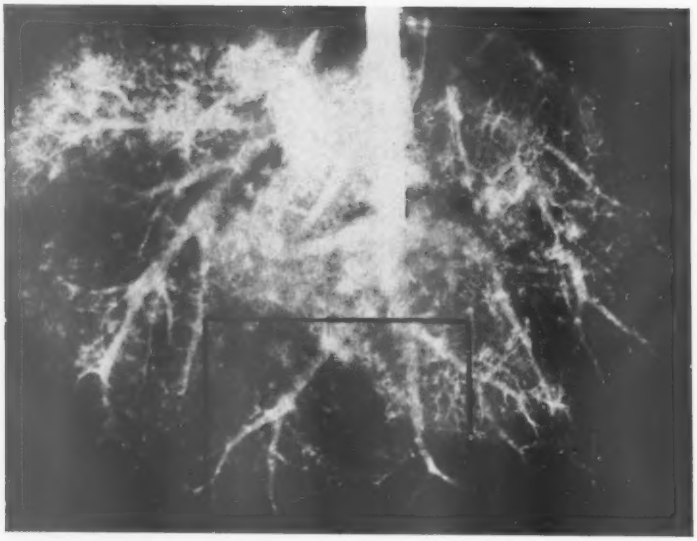

FIG. 12. Acute veno-occlusive disease. Injection of the hepatic vein with barium *post mortem*. The X-ray photograph shows that only the main branches are filled; the smaller vessels are not penetrated (P.M. No. 681: Female child aged 4 years)

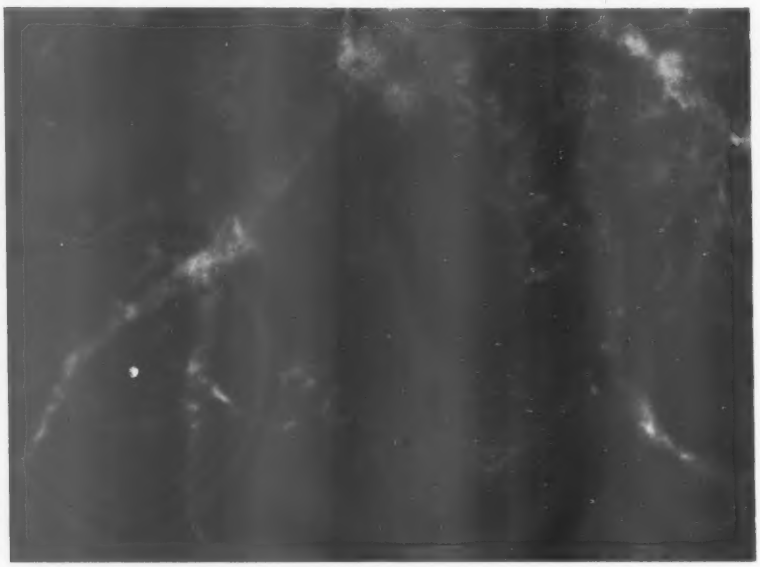

FIG. 13. Magnification of area indicated in Fig. 12

FIG. 14. No liver disease. Injection and X-ray photograph as in Fig. 12. There is complete filling of the hepatic venous tree, including the smallest branches (P.M. No. 689: Female child aged 6 years)

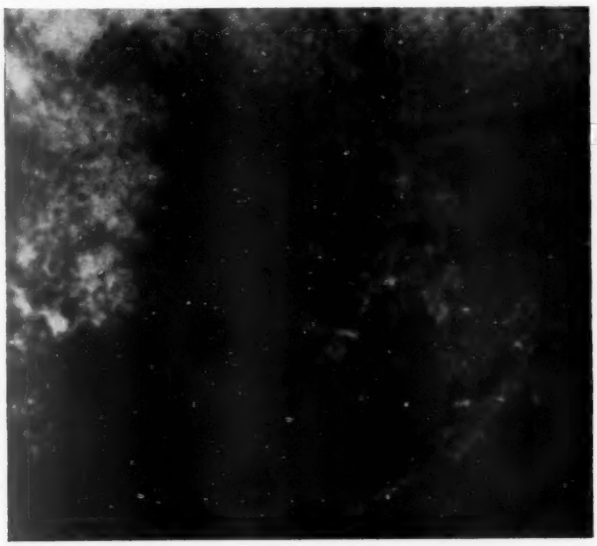

FIG. 15. Magnification of area indicated in Fig. 14

616.455–006:616.61

PRIMARY ALDOSTERONISM[1]

By M. D. MILNE, R. C. MUEHRCKE, and IAN AIRD

(From the Departments of Medicine and Surgery, Postgraduate Medical School of London)

With Plates 32 and 33

Hypokalaemic weakness or paralysis due to excessive loss of potassium in the urine was first described by Brown, Currens, and Marchand (1944) in cases of renal tubular acidosis. Later it was found that identical symptoms could occur in the de Toni-Fanconi syndrome (Milne, Stanbury, and Thomson, 1952; Bickel, Smallwood, Smellie, and Hickmans, 1952), and after uretero-sigmoidostomy (Diefenbach, Fisk, and Gilson, 1951). All the patients so described were acidotic, with reduction of both plasma-potassium and plasma-bicarbonate. The urinary loss of potassium could be explained as an obligatory excretion of 'fixed cation' by kidneys which were inefficient in the synthesis and excretion of ammonia. Cases were also reported (Earle, Sherry, Eichna, and Conan, 1951; Evans and Milne, 1954) in which the potassium deficiency was more severe, and was associated with extracellular alkalosis and increase of plasma-bicarbonate. No satisfactory explanation of the excessive urinary loss of potassium in these patients was available until Conn (1955) described the condition of primary aldosteronism. He showed that the basic cause of the disease was an adrenocortical tumour which secreted excessive amounts of aldosterone, causing increased loss of potassium in the urine with retention of sodium. Impairment of renal function was found to be due to the resultant potassium depletion.

In the present paper we describe two cases of primary aldosteronism, with special reference to the biochemical changes during restoration of potassium before operation and after excision of the causative adrenal adenomata. The two cases were widely different in severity and mode of presentation, Case 1 showing severe periodic paralysis, while Case 2 was almost asymptomatic. A brief reference to both these patients has been published in the reports of the Section of Endocrinology of the Royal Society of Medicine (Milne and Muehrcke, 1956).

Case Reports

Case 1. The clinical history of this patient up to March 1954 has previously been reported in some detail by Evans and Milne (1954), and to avoid repetition only a brief summary of the earlier part of the illness will be given. At this time Conn's account of primary aldosteronism had not been published, and the case

[1] Received October 9, 1956.

was incorrectly diagnosed as 'potassium-losing nephritis' due to chronic pyelonephritis. The patient was a native of Nigeria and, when first seen by one of us (M. D. M.), was 41 years old. She had been in good health until 1944, when she developed a typical attack of hypokalaemic paralysis with complete flaccid quadriplegia. Between 1944 and 1953 there were repeated similar attacks, occurring about every three months. The paralysis varied in duration and severity, lasting from two to 20 days, the milder attacks involving only the legs.

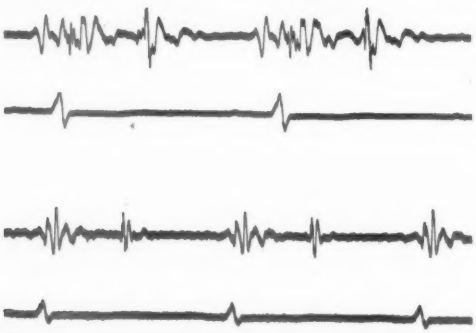

FIG. 1. Phonocardiograms recorded from the cardiac apex before (upper tracing) and after (lower tracing) adrenalectomy in Case 1. Quadruple rhythm was present before operation.

In the intervening periods there was no muscular weakness or other symptom. Between 1945 and 1947 she had had repeated attacks of acute pyelonephritis, with fever, dysuria, and frequency of micturition, and after 1950 there was constant polyuria and polydipsia, with nocturnal urinary frequency.

She was hypertensive (blood-pressure 180/110), and there was left ventricular enlargement, with an apical presystolic triple rhythm. The electrocardiogram showed evidence of both potassium deficiency and left ventricular enlargement. There was constant loss of 2 gm. of protein per day in the urine; a catheter specimen contained leucocytes, but was sterile on culture. There was complete isosthenuria, the blood-urea was in the high normal range, urea clearance was 58 ml. per minute, and endogenous creatinine clearance 65 ml. per minute. The reaction of the urine was neutral or faintly alkaline, and after ingestion of 12 gm. of ammonium chloride in four hours the minimum urinary pH was 6·6. Plasma-electrolyte concentrations in mEq. per litre were: sodium 145, potassium 1·4, chloride 87, and bicarbonate 47. There were no stigmata of Cushing's syndrome, and urinary 17-ketosteroids and 17-hydroxycorticosteroids were normal. The urinary aldosterone output was abnormally high (Cope and Garcia-Llaurado, 1954). On an intake of 285 mEq. of potassium per day the patient retained 1,000 mEq. of potassium (page 321, Fig. 2). The plasma-potassium level remained low, averaging 3·3 mEq. per litre. The isosthenuria was uninfluenced by potassium repletion, showing that it was due to irreversible renal damage, and not to the temporary nephropathy of potassium depletion (Schwartz and Relman, 1953). The patient was treated by regular potassium supplements of 110 mEq. per day, given as potassium chloride 2 gm. and potassium citrate 1 gm. three times daily. This treatment was continued for two years, and prevented any further attacks of muscular paralysis. The excess of excreted solute, 220 m.Osmol. per day, led to an increase of urinary volume, with troublesome diurnal and nocturnal frequency of micturition. The patient led an active life

until the summer of 1955, when she began to complain of increasing dyspnoea on exertion. There was evidence of left ventricular failure, the blood-pressure was unchanged, and a quadruple rhythm was audible at the cardiac apex (Fig. 1). There was radiological and electrocardiographic evidence of left ventricular dilatation and hypertrophy.

Conn (1955) had now published a preliminary account of his case of primary aldosteronism, and stated that the blood-pressure had fallen to normal after unilateral adrenalectomy. Our patient was therefore investigated by peri-renal oxygen insufflation by the presacral route, and a large adrenal tumour was demonstrated (Plate 32, Fig. 7). The right adrenal gland was removed on 20.12.1955. A posterior approach was used, since the tumour was known to be on the right side, and removal of the right adrenal gland from the front is not always easy. An incision was made along the line of the 12th rib and prolonged forward two inches from its tip. The 12th rib was excised from its bed, and the diaphragm was incised horizontally across the bed of the rib at the level of the first lumbar transverse process. The diaphragmatic incision extended outwards from the lateral border of the erector spinae. The suprarenal compartment of the perinephric box was opened in the same line, and the finger was swept around the dome-shaped upper surface of the palpably enlarged adrenal gland. The gland was then removed, together with the tumour, after serial ligation of its vessels. A small area of renal cortex was also excised. The wound was closed without drainage.

After operation the blood-pressure fell to normal values (Fig. 5, page 325). Injections of deoxycortone, 5 mg. intramuscularly, and hydrocortisone, 100 mg. in saline intravenously, were given as a precautionary measure, but in retrospect were unnecessary. Potassium supplements, which had been given up to the day of operation, were discontinued. Convalescence was uneventful except for an acute exacerbation of pyelonephritis, which was effectively treated by sulphadimidine. The blood-urea increased to a maximum value of 110 mg. per 100 ml. on the third day after operation, but had fallen to 60 mg. per 100 ml. one month later. Plasma-electrolytes were normal one week after the operation (Fig. 3, page 322). Two weeks later, however, a considerable acidosis had developed, the plasma-bicarbonate level falling to 19 mEq. per litre, and was corrected by oral sodium bicarbonate. Although the isosthenuria persisted, the daily urinary volume was reduced (Fig. 5) because of decrease of the osmotic load excreted. Protein loss in the urine had fallen to 250 mg. per day after two weeks (Fig. 5). There was a decrease of 1·5 cm. in the transverse diameter of the heart, and the heart sounds were restored almost to normal (Fig. 1). The blood-pressure remained normal for two months, but had risen to 180/110 four months after the operation. The patient was favourably impressed by an improvement in effort tolerance, and by the relief of polyuria after cessation of potassium supplements. Her return to Nigeria has prevented further observation.

Case 2. This patient, a widow aged 60 years, had always been healthy, and can be described as an almost asymptomatic case of primary aldosteronism. She consulted her general practitioner complaining of a mild and transient occipital headache. Physical examination revealed a mild hypertension (blood-pressure 180/110) and slight proteinuria. Chest X-rays showed moderate left ventricular enlargement. The electrocardiogram was suggestive of potassium deficiency, there being depression of the S–T segment, flattening of the T waves, and appearance of U waves in the left precordial leads. Plasma-electrolyte values in mEq. per litre were: sodium 145, potassium 2·0, chloride 95, and

bicarbonate 40. The patient was re-examined at monthly intervals for the next six months, and the electrocardiographic and biochemical abnormalities were unchanged. The patient denied any symptoms of muscular weakness, but admitted slight dyspnoea on effort. Renal function was slightly impaired, the blood-urea being 35 mg. per 100 ml., creatinine clearance 65 ml. per minute, and maximum urinary specific gravity 1,016. The salivary Na/K ratio was consistently below 0·3, which was thought to favour a diagnosis of primary aldosteronism. Peri-renal oxygen insufflation with tomography failed to show any abnormality, and determination of urinary steroids, including aldosterone, gave normal values. Potassium chloride, 200 mEq. daily, was given in divided doses by mouth, and 400 mEq. of potassium were retained in three days (Fig. 2). The plasma-electrolytes returned to normal values: plasma-potassium increased to 4·5 mEq. per litre, and plasma-bicarbonate decreased to 29 mEq. per litre. These values were maintained throughout the next four months by a daily supplement of 110 mEq. of potassium—potassium chloride 2 gm. and potassium citrate 1 gm. three times daily.

At this stage the diagnosis was reconsidered. The two possible alternatives were 'potassium-losing nephritis' without adrenal disease, and primary aldosteronism. Kidney tissue obtained by percutaneous renal biopsy was histologically normal. This finding was strongly in favour of primary aldosteronism. The patient was given the choice of continued medical palliative treatment or radical cure by operation, and she preferred surgery. No evidence was available to indicate the side on which the tumour might lie, and accordingly it was decided to explore both adrenal glands simultaneously. For this purpose an anterior transabdominal approach is suitable. The abdomen was opened by an oblique upper abdominal incision, a hand's breadth below and parallel to the right costal margin. The incision extended from the lateral border of the right rectus across the mid-line to meet the left costal margin. The right rectus and its sheath, the linea alba, and the inner portion of the left rectus muscle and its sheath, were divided in the line of the skin incision, and the abdominal cavity was opened, with division of the ligamentum teres. It was decided to explore the left adrenal gland first. An incision was made through the posterior peritoneum and retroperitoneal fascia just lateral to the lieno-renal ligament, and the spleen, together with the tail and body of the pancreas and the splenic vessels, was mobilized forwards and to the right. Gentle traction on the spleen exposed the left adrenal gland but, although a good view was obtained of the gland, it was still uncertain whether a tumour lay in it. The gland was now mobilized forwards, still attached to its middle artery and main vein, by circumferential dissection, and a tangential view of the gland was obtained. It was then obvious that the normal flatness of each of the surfaces of the gland was replaced by a central convexity, and it seemed reasonably certain that it was the seat of a tumour, although the disturbance of contour was not very great. Before removal of the left adrenal gland was pursued further, the gland on the right was examined. The right kidney was drawn downwards, an incision was made in the posterior peritoneum of Morrison's hepato-renal pouch, and the right adrenal gland was displayed. Its contour was followed upwards and medially behind the edge of the inferior vena cava, and the gland both to vision and to palpation was clearly of a normal size and shape. The left adrenal gland was accordingly removed, with separate ligation of its vessels. On transection after removal, a central yellow tumour was clearly visible (Plate 32, Fig. 8*b*). Even on section the normal flatness of the left adrenal gland was not grossly disturbed. A further renal biopsy was obtained.

Convalescence was completely uneventful. No potassium supplements and

no adrenal steroids were given after operation. Plasma-electrolytes have since remained within normal limits, and the urine has become virtually free of protein (Fig. 5). The blood-pressure fell to normal levels after operation (Fig. 5), but had risen to 180/105 four months later. There was a reduction of 1 cm. in the transverse diameter of the heart, and effort tolerance was improved. The blood-urea increased to a maximum value of 75 mg. per 100 ml. on the sixth

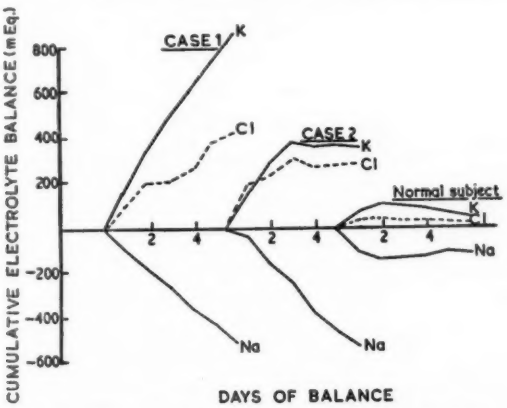

FIG. 2. Cumulative balances of potassium, sodium, and chloride during the first six days of potassium repletion (200 mEq. KCl per day) in two cases of primary aldosteronism. The changes are compared with those found in a normal subject on the same potassium intake.

day after operation, but had returned to normal after three weeks. There was no significant improvement in urinary concentrating power, the range of specific gravity being 1,005 to 1,018. The patient was favourably impressed by the increase in effort tolerance, and by the fact that potassium supplements were no longer necessary.

Special Investigations

1. *Histology of the adrenal glands and kidneys.* Both the excised tumours were well-encapsulated adrenal cortical adenomata. The tumour in Case 1 was deep orange in colour, its diameter 2·8 cm., and the total weight of the excised adrenal gland 12 gm. The adenoma had almost completely replaced the gland, a small amount of unaffected cortex remaining at the apex (Plate 32, Fig. 8*a*). The tumour consisted of large lipoid-containing cells, with no evidence of malignancy (Plate 33, Fig. 9). The nuclei were variable in size, but showed no mitoses. The adenoma in Case 2 was canary-yellow in colour, 14 mm. in diameter, and the total weight of the excised adrenal gland 5 gm. The histological appearance was similar to that found in Case 1, but the tumour-cells were rather smaller (Plate 33, Fig. 9). Histochemically the tumours showed an unusually strong reaction for alkaline phosphatase in the stromal vessels. The unaffected adrenal cortex was atrophied, especially the zona glomerulosa.

Histological examination of the kidney in Case 1 showed gross fibrous scarring

and loss of parenchyma (Plate 33, Fig. 10). Many glomeruli were hyalinized, and there was periglomerular fibrosis and arteriolar endarteritis. Small collections of 'thyroid-like tubules' suggested a pyelonephritic aetiology. Renal tissue obtained at operation in Case 2 showed somewhat more renal abnormality than had been found in the smaller amount of tissue obtained by percutaneous biopsy before operation. There were some scarred glomeruli, and the vessel

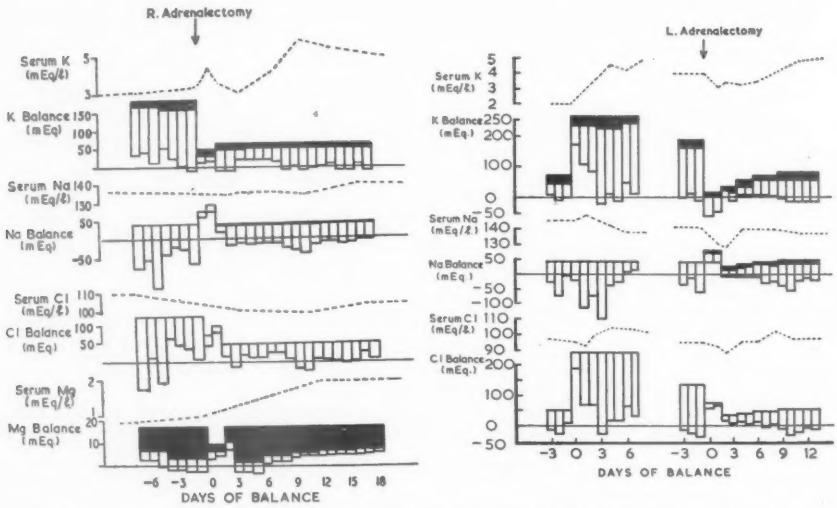

FIG. 3. Plasma levels and balance of potassium, sodium, chloride, and magnesium in two cases of aldosteronism. In Case 1 (left) right adrenalectomy was performed on the eighth day of the balance. The balances in Case 2 (right) include potassium repletion before operation in addition to the effects of adrenalectomy. Intake is plotted upwards. Faecal output (black) and urinary output (clear columns) are plotted downwards from the intake.

walls were thickened, with reduplication of the elastic laminae. The changes appeared to be ischaemic in origin, and were similar to those seen in many cases of benign essential hypertension in persons of this patient's age.

2. *Hormonal analyses of urine and tumours.* The urine in Case 1 was shown to contain an abnormal amount of a steroid, which on chromatography was typical of aldosterone (Cope and Garcia-Llaurado, 1954). An extract of the tumour injected into rats which had undergone adrenalectomy caused a fall of the urinary Na/K ratio. The urine in Case 2 showed only slight sodium-retaining effect on bio-assay by the method of Johnson (1954). Chromatographic analysis for aldosterone was performed by Dr. I. H. Mills, at St. Thomas's Hospital, on two 24-hour specimens, and a high normal result was obtained. The excised tumour in Case 2 was examined by Mrs. S. A. Simpson and Dr. J. F. Tait at the Middlesex Hospital. After incubation the tumour tissue produced twice as much cortisol, five times as much aldosterone, and eight times as much corticosterone as an equal weight of ox adrenal gland. A similar incubation was unfortunately not performed in Case 1.

3. *Electrolyte balance after potassium repletion.* All balance studies were performed in the metabolic ward. The diet and all dietary rejects were analysed, in addition to urine and faeces. Urine was analysed daily, and faeces as three-day pooled specimens. Both patients were initially treated by daily potassium chloride supplements (200 mEq. per day). Fig. 2 gives the cumulative balances of potassium, sodium, and chloride in both patients, and in a normal subject on an identical régime. Patient No. 1 retained 800 mEq. of potassium in six days, and a further 200 mEq. were retained in the next two weeks. Patient No. 2 retained 400 mEq. of potassium, almost all in the first three days. Both patients lost about 500 mEq. of sodium, which must have been derived from the intracellular compartment, since the simultaneous chloride balance was strongly positive. In Case 2 the plasma-electrolytes were restored to normal concentrations (Fig. 3), but in Case 1 the plasma-potassium level remained abnormally low in spite of the large intake of potassium. Acid-base balance was not studied in detail in Case 1, but the plasma-bicarbonate level fell to normal after potassium repletion. Case 2 showed the neutral or faintly alkaline urine which has been stated to be typical of primary aldosteronism (Dustan, Corcoran, and Page, 1956). Acid-base balance was maintained by an abnormally high ammonia output. The acid-ash value of the balance diet was calculated to be 45 mEq. per day; over 90 per cent. of this was excreted as ammonia, and less than 10 per cent. as titratable acidity. After repletion with potassium chloride the urine became strongly acid at pH 5·2, and now 60 per cent. of the total hydrogen-ion excretion was accounted for by titratable acidity, and only 40 per cent. by ammonia. The ammonia output was reduced in spite of an increased urinary acidity. Reasons are given later for regarding these changes as due to potassium depletion, and not directly to primary aldosteronism.

4. *Electrolyte balance after adrenalectomy.* In both cases adrenalectomy was performed after prolonged ingestion of potassium supplements, which had almost fully corrected the potassium deficiency. Patient No. 1 retained only 100 mEq. of potassium in the first nine days after operation; no additional potassium was retained in Case 2 (Fig. 3). Both patients showed a progressive increase of plasma-potassium after operation, maximum values being reached on the 12th day. This fact indicated that the reduction of plasma-potassium before the adrenalectomy was due not to potassium deficiency, but to the action of excess of aldosterone. In both patients there was a normal metabolic response to surgery, sodium and chloride being retained in the first two days after operation (Fig. 3). In Case 1, because of the severe renal damage and isosthenuria, the low output of sodium chloride was almost entirely due to oliguria following the operation. In Case 2 there was reduction of both urinary volume and sodium-chloride concentration. After the period immediately following operation the sodium balance became negative, although chloride was retained (Fig. 3), again indicating that sodium was being lost from the intracellular compartment. Patient No. 1 lost 280 mEq. of sodium, and Patient No. 2 220 mEq. Muscle biopsy specimens obtained at operation confirmed the fact that there was an excess of intracellular sodium (Table I). In Case 1 the serum-magnesium level

was below normal (Fig. 3), but rapidly increased after operation, a maximum value being reached on the 12th day. This change was associated with a positive magnesium balance, 70 mEq. being retained in the first three weeks. The urinary magnesium level was high before operation, but fell to low values afterwards. Although magnesium excretion in Case 2 was a little reduced after operation, there was no significant change either in serum-magnesium values or

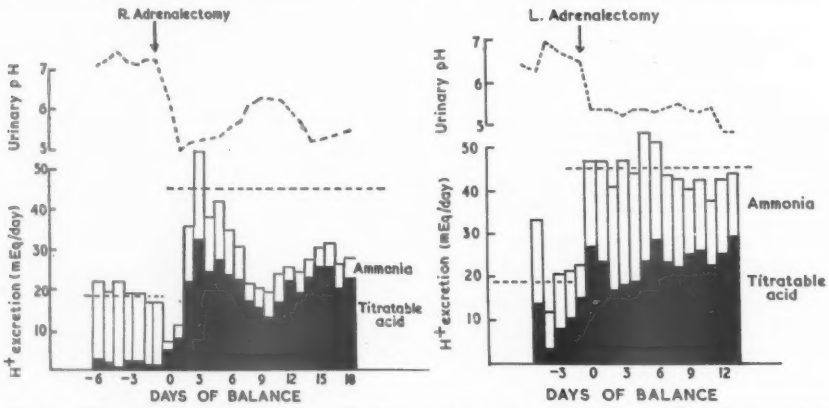

FIG. 4. Urinary pH and excretion of hydrogen ion in two cases of primary aldosteronism before and after adrenalectomy. The horizontal broken lines give the calculated acid-ash value of the experimental diet. In Case 1 (left) excretion of ammonia after operation is insufficient to maintain acid-base balance. In Case 2 (right) excretion of hydrogen ion is normal throughout.

TABLE I

Electrolyte Content of Skeletal Muscle

	mEq. per gm. of fat-free dry solid		
	Na	*K*	*Cl*
Case 1	22·0	39·0	9·0
Case 2	15·5	40·5	7·5
Normal values . . .	11·4–11·9	43·5–48·1	6·6–7·1

The normal values are taken from Mokotoff, Ross, and Leiter (1952).

magnesium balance. Case 1 showed a positive calcium balance after operation; the urine became virtually free of calcium. Although 75 mEq. of calcium were retained, the serum-calcium level remained normal throughout. Correspondingly, the phosphate balance was slightly positive, but less so than was expected from the calcium retention, owing to a loss of nitrogen after operation. Case 2 did not show any significant change in calcium or phosphorus balance, and the urine after operation always contained considerable amounts of calcium.

Before operation the acid-ash value of the diet was only 18 mEq., because the patients were taking 27 mEq. potassium citrate daily. After operation the acid-ash value was increased to 45 mEq., since potassium supplements were no longer necessary. In both patients the urine became strongly acid after adrenalectomy (Fig. 4), showing that there was no reduction of the power of urinary

CLEARANCE VALUES (ml/min.)

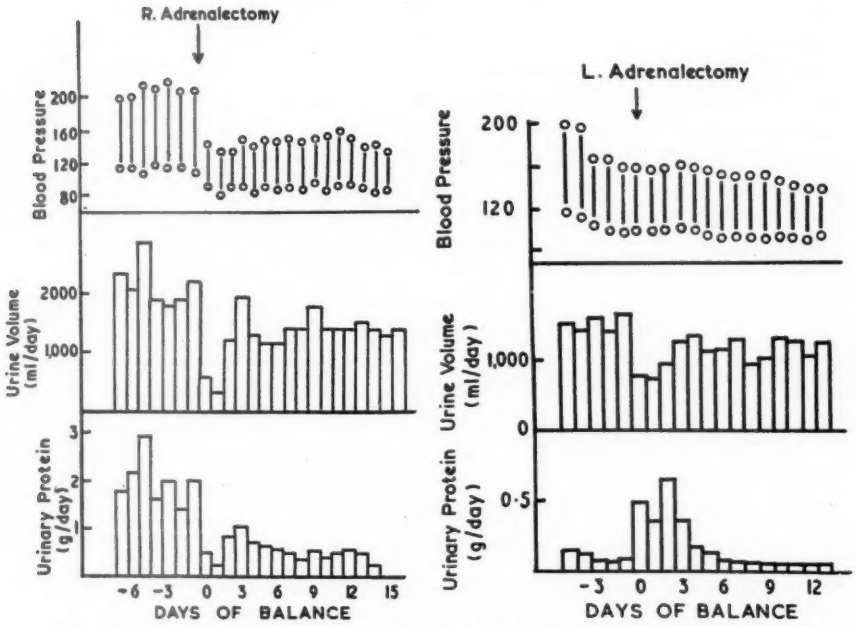

FIG. 5. Blood-pressure, urinary volume, and daily urinary protein loss before and after adrenalectomy. Case 1 on left; Case 2 on right.

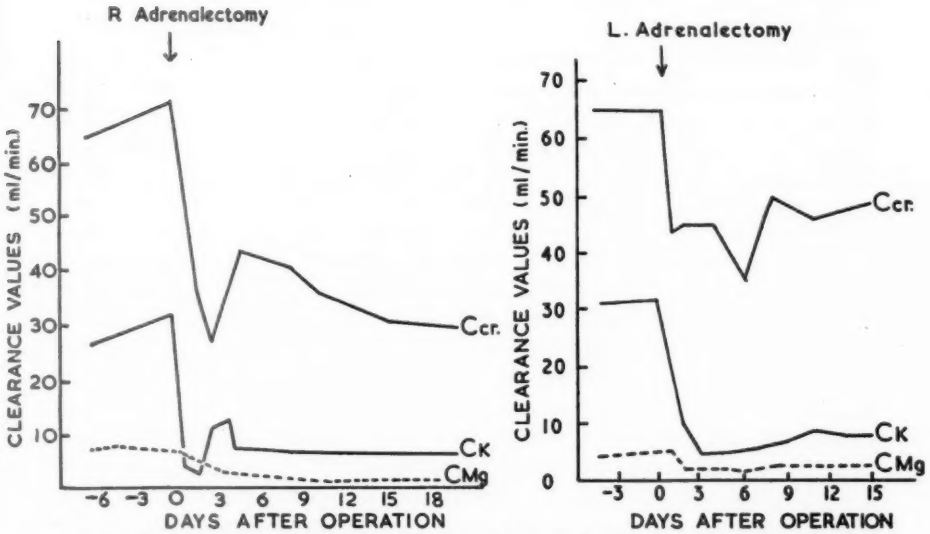

FIG. 6. Clearances of creatinine, potassium, and magnesium before and after adrenalectomy. Case 1 on left; Case 2 on right. The clearances of creatinine and potassium were reduced after operation in both patients. Magnesium clearance decreased in Case 1.

acidification. Ammonia synthesis in Case 1, however, was grossly inadequate, and the excretion of hydrogen ion was insufficient to maintain acid-base balance (Fig. 4). The excretion of sulphate was higher than that of hydrogen ion, often by as much as 10 mEq. daily. A progressive acidosis therefore occurred, and one month after operation the plasma-bicarbonate level had fallen to 19 mEq. per litre. This defect was corrected by oral sodium bicarbonate. In contrast,

TABLE II

Effect of Adrenalectomy on the Faecal Na/K Ratio

	Case 1	*Case 2*
Average Na/K ratio before operation .	0·11	0·04
Na/K ratio in the first three days after operation	0·52	0·72
Average Na/K ratio after operation . .	0·50	0·57

Patient No. 2, with relatively undamaged kidneys, was able to maintain a normal acid-base balance (Fig. 4). Ammonia excretion was normal, and the output of hydrogen ion always exceeded that of sulphate.

5. *Proteinuria and renal clearances.* In Case 1 proteinuria was considerable before operation, but decreased afterwards (Fig. 5). Proteinuria in Case 2 was barely detectable by the usual clinical tests, but increased considerably in the first four days after operation, possibly owing to slight traction on the renal pedicles during exposure of the adrenal glands. It subsequently fell to below the levels found before operation, and no protein could be detected by the usual tests. Fig. 6 gives the clearances of creatinine, potassium, and magnesium after adrenalectomy. In both cases there was a depression of creatinine clearance after operation; in Case 2 it had returned to the previous levels after two months, but in Case 1 renal function remained depressed; the blood-urea finally became steady at 60 mg. per 100 ml. The sharp fall in potassium clearance in both patients after operation was due partly to cessation of potassium supplements, and partly to excision of the tumour. Magnesium clearances showed a smaller but similar fall after operation.

6. *The electrolyte composition of saliva and faeces.* Specimens of saliva were collected by getting the patients to chew paraffin wax. The volumes were always between 1·6 ml. and 2·4 ml. per minute. Na/K ratios before operation were consistently below 0·3 in both patients. A minimum value of 0·13 was recorded on one occasion in Case 2. After operation the ratio slowly increased, and three weeks later was 0·58 in Case 1 and 0·50 in Case 2. In another two months the ratios had risen to 0·85 and 1·20 respectively. In contrast to this slow rise in the salivary Na/K ratio, there was an abrupt increase of the corresponding faecal ratio (Table II). Faecal sodium levels were abnormally low before operation, but reached high normal values immediately after adrenalectomy. There was no significant change in faecal potassium. No observations were made on the electrolyte content of thermal sweat.

Discussion

Only nine examples of primary aldosteronism have been described in detail (Conn and Louis, 1956; Mader and Iseri, 1955; Foye and Feichtmeir, 1955; Chalmers, FitzGerald, James, and Scarborough, 1956; Crane, Vogel, and Richland, 1956; van Buchem, Doorenbos, and Elings, 1956; Campbell, Nicolaides, and Steinbeck, 1956; Eales and Linder, 1956; Hellam, 1956); but a brief summary of other cases has been published by Dustan, Corcoran, and Page (1956). All except two have been due to an adrenal cortical adenoma; in one case an adrenal cortical carcinoma was found (Foye and Feichtmeir, 1955), and a second was due to bilateral cortical hyperplasia (van Buchem, Doorenbos, and Elings, 1956). All the reported patients have been hypertensive, and have given a history of muscular weakness or periodic paralysis. Case 1 is a typical example of the disease. The duration from the onset of symptoms to excision of the tumour was 12 years, which is the longest yet recorded. Since no effective therapy was given for 10 years, the condition seems to be relatively benign, provided the blood-pressure does not rise to dangerous levels, as in the case described by Chalmers, FitzGerald, James, and Scarborough (1956). Case 2 is the first case of asymptomatic primary aldosteronism to be described. Both hypokalaemia and hypertension were found, but neither had produced any obvious symptoms. Presumably all cases of the disease must pass through a similar phase before the potassium deficiency becomes severe enough to be clinically obvious. Potassium deficiency of a similar order (loss of 400 mEq. of potassium) has been produced experimentally without causing any subjective effects (Black and Milne, 1952; Fourman, 1954). In all proved cases of primary aldosteronism the patients have had a raised blood-pressure. Luft, Ringertz, and Sjögren (1951) described a patient, diagnosed as having 'cryptogenic hypokalaemia', in whom the blood-pressure was normal throughout. This patient suffered from muscular weakness, and at necropsy a small adrenal cortical adenoma with atrophy of the zona glomerulosa was found. In retrospect this case is almost certainly an example of primary aldosteronism. Therefore neither hypertension nor muscular weakness are essential features of the disease, and cases must exist in which the sole abnormality is a symptomless potassium deficiency.

In the patient of Chalmers, FitzGerald, James, and Scarborough (1956), and in our Case 2, urinary aldosterone was within normal limits. With present analytical techniques the finding of a normal aldosterone output does not exclude the diagnosis. The tumour in Case 2 was capable of synthesis of corticosterone as well as aldosterone. Corticosterone has both gluco-corticoid and mineral-corticoid effects (Dorfman, 1954). After adrenalectomy in Case 1 there was retention of calcium, instead of the more usual loss of calcium after operation. A similar finding occurs in Cushing's syndrome, in which osteoporosis from excessive production of glucocorticoids is a prominent feature. There is increasing evidence that the various clinical syndromes produced by adrenal cortical tumours are often not sharply defined. Intermediate cases, showing

features of both the adrenogenital syndrome and Cushing's syndrome, are not infrequent; many cases of Cushing's syndrome are complicated by hypokalaemia and potassium deficiency; and some examples of primary aldosteronism show evidence of gluco-corticoid excess (Foye and Feichtmeir, 1955; Mader and Iseri, 1955).

In both our patients there was retention of sodium and chloride after operation, as seen in any severe surgical procedure (Moore and Ball, 1952). The immediate change in the faecal Na/K ratio in both patients suggests that excessive aldosterone production had been suppressed by the adrenalectomy. These results therefore support previous views (Robson, Horn, Dudley, and Stewart, 1955; Wilkinson, 1956) that salt retention after operation is not dependent on adrenal function and mineral-corticoid excess.

Both patients showed the abnormalities of plasma-electrolytes which are typical of primary aldosteronism. Reduction of plasma-potassium and increase of plasma-bicarbonate are excessive when compared with other types of potassium deficiency. Cheek and West (1956) have shown that deoxycortone injected into potassium-depleted rats causes a retention of sodium in the extracellular compartment, with consequent exaggeration of hypokalaemic alkalosis and increase of plasma-bicarbonate. Aldosterone seems to have the same effect in primary aldosteronism. Reduction of plasma-potassium is due partly to potassium deficiency from excessive urinary loss, and partly to an extrarenal action of the hormone, which influences the distribution of cation between the extracellular and intracellular compartments. In both our patients adrenalectomy caused a considerable increase of plasma-potassium, although retention of potassium was negligible. Woodbury (1953) found that deoxycortone, injected into rats which had undergone nephrectomy, caused an increase of plasma-sodium, but had no effect on plasma-potassium. The changes found in primary aldosteronism suggest that in similar circumstances aldosterone would lower plasma-potassium, as well as increasing plasma-sodium. Ingestion of potassium chloride in Case 2 restored the plasma-electrolytes to normal, but in Case 1 the levels of both potassium and magnesium in the plasma remained abnormally low. Reduction of plasma-magnesium has previously been reported in the case of Mader and Iseri (1955). Since in Case 1 there was magnesium retention after adrenalectomy, the low plasma levels were at least partly due to magnesium depletion from excessive loss in the urine. Conway (1956) considered that adrenal cortical hormones may influence magnesium metabolism in a similar manner to that of potassium.

Dustan, Corcoran, and Page (1956) have claimed that a neutral or faintly alkaline urine is characteristic of primary aldosteronism. It occurs, however, in potassium deficiency from other causes. The potassium-deficient kidney contains excessive amounts of glutaminase and aminoacid oxidase (Iacobellis, Muntwyler, and Griffin, 1954), with a consequent increase of ammonia synthesis. A greater proportion of hydrogen ion is therefore excreted as ammonia, with reduction of titratable acidity and increase of urinary pH. Potassium repletion rapidly reduces both ammonia synthesis and urinary pH (Milne, Muehrcke, and

Heard, 1957). After adrenalectomy the urine became strongly acid in both our patients. Excretion of hydrogen ion was normal in Case 2, and the plasma-bicarbonate remained normal. The damaged kidneys of Case 1 were unable to synthesize enough ammonia to maintain acid-base balance, and a metabolic acidosis developed. There were extreme fluctuations in plasma-bicarbonate in this patient. Before therapy the plasma-bicarbonate was 47 mEq. per litre, and one month after adrenalectomy 19 mEq. per litre.

The interrelation of renal and adrenal function in primary aldosteronism is complex, but of great clinical interest and importance. Potassium deficiency can cause both structural and functional abnormalities in the kidney (Follis, Orent-Keiles, and McCollum, 1942; Schwartz and Relman, 1953). The structural changes can be assessed in life only by renal biopsy. Three grades of severity can be recognized: no histological abnormality, reversible changes specific of potassium deficiency, and irreversible renal lesions. In Case 2 there were functional defects, but no histological changes except those secondary to hypertension. Conn and Louis's patient (1956) showed reversible lesions, while irreversible damage was found in our Case 1 and in the patient described by Chalmers, FitzGerald, James, and Scarborough (1956). In Case 1 the clinical history suggests that the potassium deficiency due to primary aldosteronism preceded the pyelonephritis. The two conditions are probably not merely coincidental. Pyelonephritis was also found in the case of primary aldosteronism reported by Eales and Linder (1956), and it is not infrequent in prolonged potassium deficiency from other causes (Jensen, Baggenstoss, and Bargen, 1950; Relman and Schwartz, 1956). Potassium depletion reduces the renal blood-flow (Schwartz and Relman, 1953), and causes necrosis of proximal tubule cells (Follis, Orent-Keiles, and McCollum (1942), both of which factors may increase the risk of bacterial infection. There is some evidence that magnesium depletion may cause renal lesions (Greenberg, Lucia, and Tufts, 1938), and it is possible that this factor was also involved in production of the nephropathy in Case 1. The reverse sequence of pyelonephritis causing secondary aldosteronism may also occur. Chronic pyelonephritis may lead to 'salt-losing nephritis' (Enticknap, 1952), which causes adrenal cortical hyperplasia and excessive secretion of aldosterone (Luetscher, 1956). This in turn may produce potassium deficiency and hypokalaemia. Bartter (1956) has suggested that salt deprivation may help in differential diagnosis, patients with primary aldosteronism being able to excrete a urine containing minimal amounts of sodium. This test would have been misleading in Case 1, in which the associated pyelonephritis prevented efficient conservation of sodium. In addition, Mahler and Stanbury (1956) have shown that severe potassium deficiency may of itself reduce the capacity of the kidney to retain sodium.

The diagnosis of primary aldosteronism. There are three steps in the diagnosis of primary aldosteronism: (1) Proof that the patient is deficient of potassium. (2) Proof that the deficiency is due to excessive urinary loss of potassium. (3) Decision whether the deficiency is due to primary renal disease, or secondary to excessive production of aldosterone by the adrenal cortex. The first two steps

can readily be taken by subjecting the patient to a potassium-balance test with added potassium supplements. The third is unfortunately much more difficult, because of the complex interrelation of renal and adrenal function. Although it is too early to be dogmatic, the following investigations are considered of value.

(*a*) *Plasma electrolytes.* In primary aldosteronism the plasma-potassium tends to be lower, and the plasma-bicarbonate higher, than would be expected from the degree of potassium depletion. In retrospect, the electrolyte changes in Case 2 were diagnostic of the disease. A potassium deficit of only 400 mEq. would be expected from experimental evidence (Black and Milne, 1952; Fourman, 1954) to be associated with a plasma-potassium level of about 3·0 mEq. per litre and a plasma-bicarbonate level of 30 to 33 mEq. per litre. The actual values were more unequivocally abnormal. Some cases of primary aldosteronism, however, have shown an almost normal level of plasma-bicarbonate (Chalmers, FitzGerald, James, and Scarborough, 1956). The plasma-sodium is increased before treatment, while in primary renal disease low values are more common. Reduced plasma-magnesium favours the diagnosis, but normal values are of no diagnostic value. If the plasma-potassium level remains low in spite of large potassium supplements, the evidence is strongly in favour of primary aldosteronism (Case 1); if the plasma-potassium is restored to normal, no conclusion can be drawn (Case 2).

(*b*) *Renal biopsy.* Percutaneous renal biopsy may be of great value in differential diagnosis. If there is no structural abnormality, or if there are only reversible renal lesions from potassium depletion, a diagnosis of primary aldosteronism is likely (Case 2). If pyelonephritis is present the method is of no diagnostic value (Case 1).

(*c*) *Peri-renal oxygen insufflation combined with tomography.* This is a valuable method if unequivocally positive (Case 1). Adenomata of the size found in Case 2, or the even smaller tumour in the case described by Crane, Vogel, and Richland (1956), cannot be demonstrated by this technique. False positive results can unfortunately occur.

(*d*) *Evidence of increased production of mineral-corticoids.* This method cannot distinguish primary from secondary aldosteronism. Indirect evidence from analyses of saliva, sweat, and faeces can be obtained from any routine biochemical laboratory, while determination of the aldosterone output in urine is a difficult and specialized procedure. The salivary Na/K ratio varies with the volume of saliva secreted. Normal limits have been given by Prader, Gautier, Gautier, Näf, Semer, and Rothschild (1955). In the cases we have reported the faecal Na/K ratio seemed more specific, and increased more rapidly after adrenalectomy. Conn and Louis (1956) have shown that the estimation of sodium in the sweat is a further useful procedure. Estimation of urinary aldosterone may be misleading (Case 2). Excessive excretion is in favour of primary aldosteronism, since potassium deficiency from other causes tends to reduce aldosterone production (Laragh and Stoerk, 1955). Estimation of blood-aldosterone is

theoretically preferable to determination of the urinary content, but is technically difficult and of little practical value at present.

Recent reports of potassium deficiency considered to be due to primary renal disease (Jackson and Oakley, 1955; Sayers, Eyre, and Sims, 1955; Russell, Marshall, and Stanton, 1956) illustrate the difficulties of differential diagnosis. In each case reasons are given which favour the diagnosis of a primary renal lesion, but the possibility of primary aldosteronism cannot be rejected with absolute certainty. The case described by Mahler and Stanbury (1956) is of special interest because of the severity of the potassium deficiency, which amounted to 1,400 mEq. A diagnosis of primary aldosteronism was considered unlikely because of a normal aldosterone output, the presence of chronic pyelonephritis, and the restoration of plasma-potassium to a normal level after oral supplements. In addition, the adrenal glands were anatomically normal when palpated during cholecystectomy. While none of these reasons are sufficient alone to exclude primary aldosteronism, the combined evidence is strongly in favour of primary renal disease. In doubtful cases a certain diagnosis can be made only by a planned exploration of the adrenal glands. The advantage of radical surgical cure over palliative treatment with potassium supplements has to be balanced against the slight risk involved in any major surgical procedure. Exploration is the only method of excluding adrenal cortical carcinoma, as in the case described by Foye and Feichtmeir (1955). The large potassium supplements necessitated by medical treatment are inconvenient, and often produce troublesome polyuria and frequency of micturition (Case 1). In addition, adrenalectomy has usually reduced the blood-pressure and improved cardiac efficiency. In both our patients, and in the case described by Chalmers, FitzGerald, James, and Scarborough (1956), the blood-pressure had risen considerably when the patient was re-examined several months later. In some of the other reported cases observation after the operation has been too short to exclude the possibility of a similar delayed rise of blood-pressure.

Surgical exploration in cases of primary aldosteronism. The operation chosen in Case 2 showed all the advantages of an anterior approach and simultaneous exposure of both adrenal glands. The details of this operation have been described elsewhere (Aird and Helman, 1955). When the side in which the tumour exists is unknown, the anterior approach gives a good view of both adrenal glands without great disturbance to the patient. The left adrenal gland is always easy to remove from the front after the spleen and pancreas have been mobilized. Usually the right adrenal can also be removed from the front, and excision is always technically easier if an adenoma is present. The presence of a tumour in the gland makes it easier to dislodge the upper pole of the right adrenal from behind the edge of the inferior vena cava. At worst, a second operation can be done from the back for removal of the right adrenal, but we have not yet found this necessary. Had we found no tumour in Case 2, we should have wished to perform a subtotal adrenalectomy, and this can be done very conveniently by the anterior route. The whole left adrenal gland is removed, and the greater part of the right adrenal, leaving only the little tongue of tissue

at the upper pole, where the gland reaches upwards behind the medial border of the inferior vena cava, sometimes unpleasantly close to the lowest hepatic vein. Even if the site of an adrenal tumour is known, it is important to prove beyond doubt that the gland on the other side is in fact present and healthy. All these considerations persuade us that the operation of choice in primary aldosteronism is anterior transabdominal exposure of both adrenal glands.

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Summary

1. Two cases of primary aldosteronism due to adrenal cortical adenomata are described. The first patient gave a history of severe periodic paralysis for many years. The second case was virtually asymptomatic, but the patient was hypertensive and showed biochemical evidence of potassium deficiency.

2. Balance data are presented relating to the period of potassium repletion before operation and to the period following unilateral adrenalectomy. The patients were deficient of 1,000 mEq. and 400 mEq. of potassium respectively. The first patient also showed evidence of magnesium deficiency.

3. Both patients showed a normal metabolic response to surgery, with temporary retention of sodium and chloride. Very little potassium was retained after operation, although there was a considerable increase of plasma-potassium.

4. The first patient had severe chronic pyelonephritis, with considerable impairment of renal function. The second had no renal abnormalities except those referable to her hypertension.

5. The diagnosis of primary aldosteronism from potassium deficiency due to primary renal disease is discussed in detail. An anterior transabdominal exposure of both adrenal glands is considered to be the operation of choice in the former disease.

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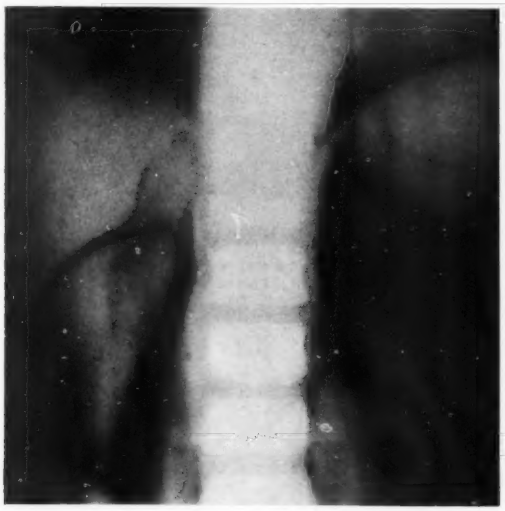


FIG. 7. Perinephric oxygen insufflation with tomography in Case 1. The right adrenal gland is greatly enlarged, while the left is normal

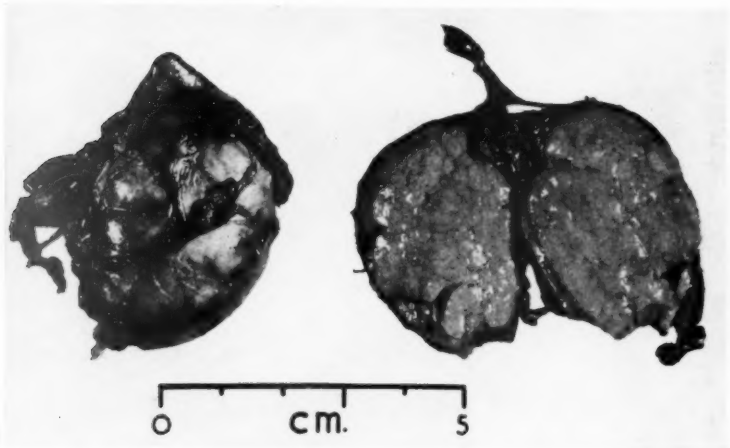
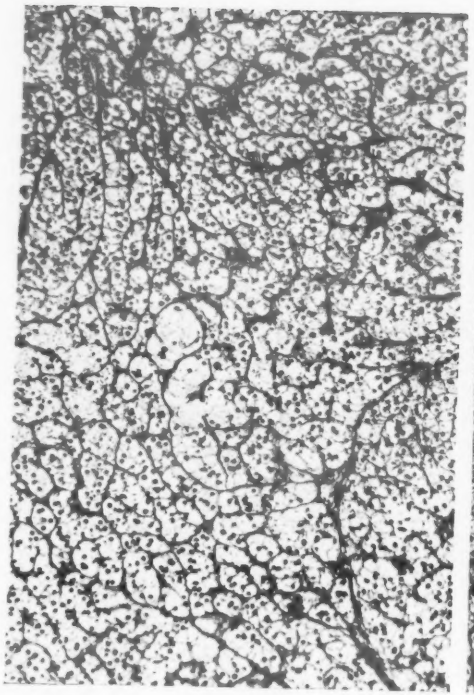
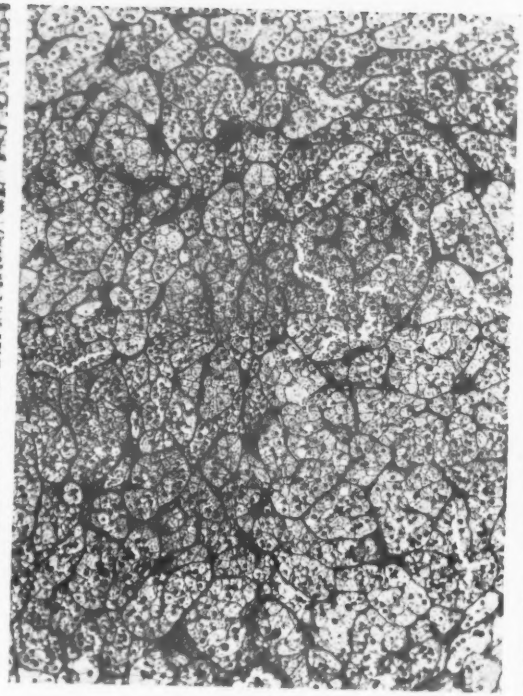


FIG. 8. Excised adrenal glands in (*a*) Case 1 and (*b*) Case 2, containing an aldosterone-secreting adenoma



Case 1



Case 2

FIG. 9. Sections of adenomata. The tumours consist of columns of large lipoid-containing cells (haemalum and eosin, ×88)

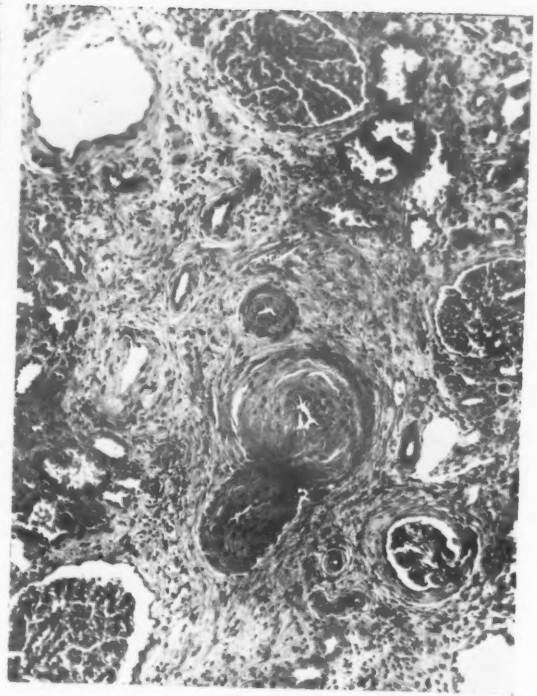


FIG. 10. Section of kidney in Case 1, showing severe chronic pyelonephritis (haemalum and eosin, ×88)

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THE IMMEDIATE TREATMENT OF CEREBRAL EMBOLISM[1]

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THE early treatment of cerebral embolism has recently become a subject for discussion and disagreement among physicians, partly owing to the use of powerful drugs and hazardous procedures in this condition, and partly because the outcome in any individual case is unpredictable until the time for immediate treatment has passed. This uncertainty in effectiveness of treatment and in accuracy of prognosis suggests the need for a controlled clinical trial, so that statistical evidence may be collected. The present study records the results of a therapeutic trial in four groups of patients, the first a control series, the second treated with repeated stellate block, the third with one stellate block and anticoagulants, and the fourth with anticoagulants alone.

Current views

Previous work and present-day views on the pathology and treatment of cerebral embolism suggest that, when the embolus becomes firmly impacted in the artery, there is an immediate reduction of blood-flow peripherally, and it is on the speed and extent of the restoration of this flow that the outcome depends. The factors influencing its restoration comprise: (1) the extent of occlusion of the collateral branches springing from the immediate neighbourhood of the embolus; (2) the degree of arterial spasm distal or proximal to the embolus; (3) the degree and duration of cerebral oedema following the embolism; and (4) the presence of consecutive thrombosis occurring on the proximal or distal side of the embolus, or both. The aim of any immediate treatment must be to combat these factors by increasing the cerebral blood-flow through and around the infarcted area, and by preventing any spread of the ischaemic process. The position is complicated by the lack of free precapillary anastomoses in the deep circulation of the brain, although there appear to be some possible arterial shunts near the surface (Young and Karnosh, 1949; Vander Eecken, Fisher, and Adams, 1952). The following methods of dealing with the immediate results of embolism have been described.

1. *Vasodilator drugs.* Many drugs with vasodilator properties have been used to increase cerebral blood-flow, but most of them appear to be ineffective. Aminophylline, nicotinic acid, and alcohol do not increase cerebral circulation in man (Wechsler, Kleiss, and Kety, 1950; Scheinberg and Jayne, 1952; Patterson,

[1] Received October 10, 1956.

Heyman, and Nichols, 1950); papaverine is apparently capable of producing a 20 per cent. increase (Shenkin, 1950–1); sodium nitroprusside and histamine, although producing cerebral vasodilatation, have no measurable effect on the cerebral blood-flow, because they also lower systemic arterial pressure (Page, 1954; Shenkin, 1950–1). Tolazoline hydrochloride ('priscol') is a powerful vasodilator, and was thought to increase cerebral blood-flow, but Scheinberg, Blackburn, and Rich (1953), using Kety's nitrous-oxide method, did not detect any alteration in normotensive patients. Clinical evidence of its use in cerebral infarction was contradictory until Clarke, Hughes-Jones, and Logothetopoulos (1954) showed clearly that intravenous tolazoline (25 mg.) had no constant effect on the cerebral blood-flow in patients with cerebrovascular disease. Smith and Turton (1951) had previously reported temporary amelioration of acute cerebral arteriosclerotic symptoms by this method of treatment. The most effective method of increasing cerebral blood-flow is by the inhalation of 5 to 7 per cent. carbon dioxide; this will produce approximately a 75 per cent. increase (Kety and Schmidt, 1948). This form of treatment, however, was used as a routine for acute cerebral infarction by Altschule (1954) in Boston without improvement in his results, and Kety (1954) has suggested that 'in acute cerebral infarction nature is using all the carbon dioxide therapy possible by means of the tremendous tension of this gas which must be accumulating in these ischaemic areas'. From the above evidence it appears unlikely that the use of vasodilator drugs can alter the natural history of cerebral embolism.

2. *Stellate ganglion block.* It has been shown in a series of both normotensive and hypertensive patients (Scheinberg, 1950) that successful bilateral stellate block produces no change in either cerebral blood-flow or cerebral vascular resistance. In spite of this work the procedure is popular in the treatment of cerebral embolism, presumably because it is expected to relieve the vasoconstriction occurring peripherally after embolism (Linton, 1941; Reynolds and Jirka, 1944; Holden, 1952), as well as the more generalized and proximal narrowing described by Villaret and Cachera (1939). This vasoconstriction may be due to collapse of the vessel wall owing to the fall in intraluminal pressure (Kinmonth, 1952; Burton, 1952), or to active arterial constriction provoked by the lodgement of the embolus (Wright and McDevitt, 1954). In either case the results of stellate block have been clinically inconclusive. Leriche and Fontaine (1934) claimed considerable success with this treatment, and even suggested that it would benefit long-established hemiplegia. Amyes and Perry (1950) reported good results in 44 cases, with electroencephalographic 'improvement', and Naffziger and Adams (1950) obtained a '59 per cent. recovery rate' in the treatment of cerebrovascular accidents. Walsh (1956) was enthusiastic about the value of stellate block in cerebral infarction, among many other conditions, and in 198 cases of cerebral catastrophe seen in general practice has found that 'approximately 50 per cent. of patients with hemiplegia following cerebral thrombosis improve after stellate block, and where improvement occurs it is so dramatic and instantaneous that it cannot be attributed only to the natural course of the disease'. There were no control subjects in his series. Millikan

(1954) has wisely stressed the importance of natural recovery, and in a small controlled series found that the patients who received stellate block for cerebral infarction fared worse than the untreated control patients, thus confirming his view (Millikan, Lundy, and Smith, 1953) that many patients who improve after stellate block would have recovered without it.

The evidence seems to show that stellate block may relax constricted vessels; but in some cases this apparent vasoconstriction is due only to lowered intraluminal pressure, and in such cases perhaps more harm than good would result. Whether the vasoconstriction due to spasm is ever sufficient to produce permanent changes is uncertain, and a controlled series of cases is needed from which data may be collected.

3. *Corticosteroid therapy.* The third condition interfering with recovery of blood-flow after infarction is cerebral oedema, and, although part of this oedema may be mechanical in origin, part of it must be produced by cellular reaction to the damaging ischaemic process. Cortisone, and recently prednisone and prednisolone, have proved themselves powerful inhibitors of cellular reaction, and it is therefore reasonable to suppose that they may effectively lessen this oedema. Russek, Russek, and Zohman (1955) reported results in 30 men and five women, suffering from recent cerebral infarction, who were treated for three weeks with cortisone in decreasing doses. There was no control group, but the authors noticed striking improvement within 24 hours in 21 patients, with amelioration of paralytic signs and beneficial changes in mental state. Whether amelioration of cerebral oedema following embolism makes any difference to the degree of permanent recovery has not been proved, and it is as well to remember the potential dangers of further thrombosis as a result of cortisone therapy (Cosgriff, 1951).

4. *Anticoagulant therapy.* It is on the value and danger of this treatment that medical opinion is sharply divided. In this country authoritative opinion is opposed to its use. Symonds (1956) has given this as his personal opinion. 'Anticoagulant drugs should not be used in cases of cerebral embolism, for in these cases haemorrhage into the area of infarction often occurs, probably as the result of displacement or fragmentation of the embolism, so that damaged vessel walls are exposed to the full force of arterial pressure.' No supporting evidence for this opinion is recorded. Brain (1954) suggested that the reason why anticoagulants have been little used in England in the treatment of cerebral vascular lesions is the possible risk that haemorrhage may occur from the area of infarction. Elkington (1955) likewise considered that, in the case of the brain, there is a risk of haemorrhage that does not exist in cases of coronary thrombosis. In North America this form of treatment is more popular, and some reliable reports are available. Wright and Foley (1947), Foley and Wright (1949, 1950), and Wright, Marple, and Beck (1948), have written of their experiences in long-term anticoagulant treatment of cerebral embolic episodes. McDevitt has also treated 57 patients of similar type without any serious haemorrhagic complications (Wright and McDevitt, 1954). On this question Wright (1954) said: 'We are particularly interested in the question of haemorrhagic infarcts,

or the result of a cerebral embolus in which the question of haemorrhage around the site of the embolus causes concern on the part of some workers. Where infarction occurs there is bleeding which is rarely if ever increased by the use of anticoagulants.' Experimental work supporting this statement was reported by Wright, Marple, and Beck in 1954, and animals receiving anticoagulants showed no increase, compared with controls, in the amount of blood around the infarction. The problem whether the advantages of anticoagulant therapy outweigh the dangers can only be settled statistically.

TABLE I

Patients with Acute Hemiplegia admitted to Ashford Hospital, showing Sex and Aetiology

Year	*Number of patients*	*Male*	*Female*	*Embolism*	*Thrombosis*	*Haemorrhage*	*Tumour*
1952	142	72	70	16	54	70	2
1953	157	77	80	18	62	74	3
1954	137	60	77	15	47	72	3
1955	139	65	74	11	56	70	2
Total	575	274	301	60	219	286	10
Per cent.	100	48	52	11	37	50	2

Patients Investigated

It was decided to record the results in all cases of cerebral embolism in patients below the age of 70 admitted to the Ashford Hospital, Middlesex, from 1952 to the end of 1955. These patients were all seen and treated personally owing to the generosity of my colleagues, and fall into four groups. In 1952 repeated unilateral stellate block was employed; in 1953 no specific treatment was given; in 1954 one stellate block was followed by anticoagulant therapy; and in 1955 anticoagulant therapy was used alone. The results as to survival and degree of recovery were collected and compared. The method of comparing historical groups is in some ways unreliable (Reid, 1954), but in conditions of infrequent occurrence where random selection is not possible, it may have value if accessory methods of treatment are consistent, and if nursing care is uniformly adequate. These conditions were present in this series. The total figures relating to hemiplegia have been analysed in Table I; the figures in all groups are very consistent, and show that haemorrhage accounted for half of the total cases, and embolism for a tenth. American figures (Murphy, 1954) differ from these, and suggest that, of all cerebrovascular accidents, cerebral thrombosis accounts for 65 per cent., embolism for 5 per cent., and haemorrhage for 20 per cent., the remaining 10 per cent. being cases of subarachnoid haemorrhage. Possibly this difference is due to the fact that the hospital concerned with the present study accepts all local patients referred to it, and also some from the wider net of the Emergency Bed Service; these unselected admissions may reflect more accurately the natural incidence of disease.

Diagnosis

The diagnosis of cerebral embolism was made on the very sudden appearance, often within seconds, of hemiplegia, hemianopia, or aphasia, in patients who

had auricular fibrillation, subacute bacterial endocarditis, recent coronary thrombosis, or mitral stenosis without fibrillation. It is of course possible for such patients to have other cerebral disorders producing hemiplegia; but when a very sudden unilateral cerebral lesion occurs during the waking hours, in a patient with a known source of potential emboli, it seems reasonable to accept the diagnosis of cerebral embolism. A lumbar puncture was done in every case

TABLE II

Patients with Cerebral Embolism

Year	*Number of patients*	*Male*	*Female*	*Average age (years)*	*Right hemiplegia*	*Left hemiplegia*	*No hemiplegia*
1952	16	5	11	52	5	10	1
1953	18	7	11	50	6	10	2
1954	15	5	10	48	5	8	2
1955	11	4	7	55	4	7	None
Total	60	21	39	51	20	35	5
Per cent.	100	35	65	..	33	58	9

in an attempt to exclude a haemorrhagic lesion. The total cases of cerebral embolism are analysed in Table II, and it is evident that the numbers, sex incidence, and average age are reasonably consistent in the four groups, although the figures are numerically small, and there is a lowered incidence of embolism in 1955. Women outnumbered men by about two to one, and embolism of the

TABLE III

Aetiology of Cerebral Embolism

Year	*Number of patients*	*Mitral stenosis and auricular fibrillation*	*Mitral stenosis*	*Auricular fibrillation (cause unknown)*	*Coronary thrombosis*	*Subacute bacterial endocarditis*	*Thyrotoxicosis and auricular fibrillation*
1952	16	8	1	2	2	2	1
1953	18	10	2	2	2	1	1
1954	15	7	1	2	4	0	1
1955	11	6	1	0	3	0	1
Total	60	31	5	6	11	3	4
Per cent.	100	52	8	10	18	5	7

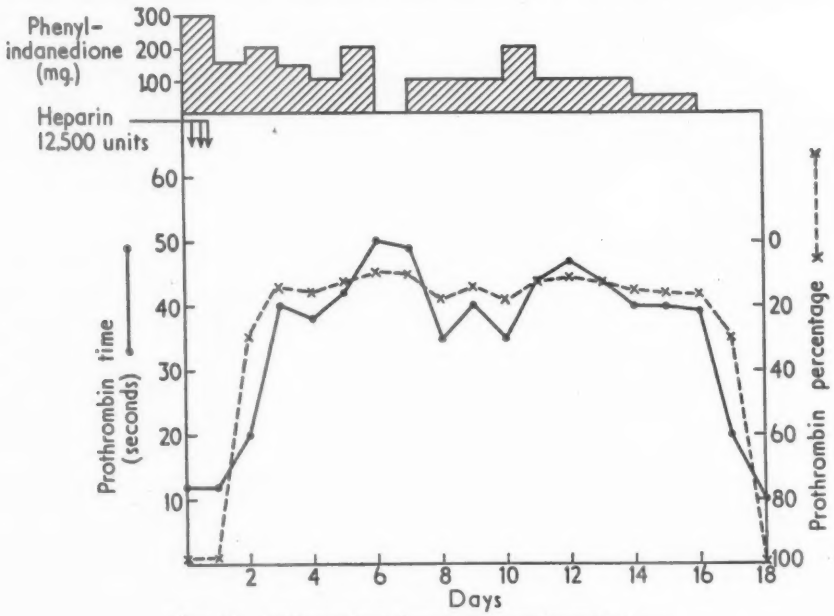
right carotid artery was nearly twice as frequent as of the left. Five patients were not hemiplegic, and showed hemianopia (two), aphasia without paresis (two) and dysarthria, dysphagia, and palatal palsy (one). The commonest cause of cerebral embolism was mitral stenosis complicated by auricular fibrillation, which accounted for more than half the cases, and if all cases of auricular fibrillation, whatever the aetiology, are taken together, they form more than two-thirds of the total (Table III).

Methods of Treatment

In 1952 unilateral stellate ganglion block was performed through the anterior approach in all cases, and repeated daily for 10 days. Between 5 and 10 ml. of 1 per cent. xylocaine were injected on the side opposite the hemiplegia

or hemianopia, and a positive Horner's sign was considered necessary to establish success. Approximately 85 per cent. of the injections produced this sign, and any return of power, vision, or speech was noted. Only the crudest tests of power were employed—the ability to raise the straight arm forward, and the length of time this position could be maintained.

In 1954 a single unilateral stellate block was performed immediately on admission, usually within 24 hours of the embolism, and often within 12 hours,



Case 51. Anticoagulant dosage and prothrombin time.

as the catastrophic onset usually accelerated admission to hospital. Six hours later, 12,500 units of heparin were given intravenously, followed by two similar doses intramuscularly at six-hourly intervals; with the first dose of heparin oral anticoagulant therapy was begun, and continued for 14 days. The heparin dosage was at first controlled by clotting-time estimation, but this was quickly found to be unnecessary, as consistent results were obtained, and the treatment was too short to be dangerous. The oral anticoagulant chosen was phenylindanedione ('dindevan'), which takes effect in about 18 hours, so that a continuous anticoagulant effect was maintained from the beginning by combining it with heparin. Biscoumacetate ('tromexan') has very much the same action, but is more expensive, and the drugs with more prolonged action, such as dicoumarol, were considered less suitable, as their effects are slower in onset and continue long after treatment has stopped. The dosage of phenylindanedione was 300 mg. in divided doses for the first 24 hours, 200 mg. for the next 24 hours, and then usually between 100 and 150 mg. daily according to the prothrombin time. The prothrombin time was maintained at from three to four times the

control (usually 12 seconds), so that the prothrombin level remained between 10 per cent. and 30 per cent. of normal. A typical chart with dosage is shown in the accompanying figure.

In 1955 the anticoagulant therapy was continued as above, but the stellate block was no longer performed, so that heparin and phenylindanedione could be given immediately on admission. In addition, some modification of the dosage of anticoagulants was made for elderly and for hypertensive patients.

Dangers of Anticoagulant Therapy

There are three dangers which have already been partly discussed, and which are probably the reason for such treatment being unpopular in this country. First, accurate diagnosis is essential, and only patients in whom the diagnosis is certain should be treated. The criteria for diagnosing cerebral embolism have already been stated, and the advisability of lumbar puncture, carefully performed, is stressed. Secondly, the danger of bleeding into and around the infarct worries many physicians. This point has already been discussed; some consider, without much evidence, that bleeding is a dangerous probability, but the experimental evidence is contrary to this belief. Seven patients treated with anticoagulants died, four of them while the prothrombin time was satisfactorily prolonged. At the autopsies there was no sign of intracranial bleeding, and the infarcted areas were surrounded by the usual small area of haemorrhage. Thirdly, there is the danger of bleeding elsewhere in the body if the anticoagulant therapy is allowed to get out of control. Possibly age plays some part in this occurrence, and it may be wiser to keep the prothrombin time down to between two and three times the normal in patients over the age of 60 or 65. The other factor which limits full dosage is hypertension, and in the 1955 series patients whose systolic pressure was above 180, or whose diastolic pressure was above 110, were not allowed a prothrombin time above 36 seconds. There was one case in the 1954 series which was very disturbing, as control was lost quite unexpectedly.

Case 43. A woman aged 68 years was admitted with a history of sudden onset of right hemiplegia, aphasia, and hemianaesthesia four hours previously. The heart was fibrillating, and she had had an attack of left mammary pain four weeks previously. A left stellate block was done, and anticoagulant therapy commenced. On the ninth day the prothrombin time was found to be 60 seconds, having been only 39 seconds the day before; although anticoagulants were discontinued at once, it rose to 110 seconds, and haematuria occurred. In spite of treatment with vitamin K the haematuria continued; the patient became uraemic, and died on the 14th day of treatment, without any improvement of her hemiplegia. At autopsy there was an extensive cardiac infarction, with mural clot, and an embolus had plugged the left middle cerebral artery close to its origin. No haemorrhage was found in the brain or at the site of stellate block, but the kidneys showed extensive bleeding, and each pelvis was full of blood-clot.

There can be no doubt that this patient's death was caused or accelerated by anticoagulant therapy, and after this occurrence patients over the age of 60 received a modified dose, to ensure stricter control at a lower anticoagulant level.

In addition, the danger of a haematoma in the neck from the stellate block has to be considered. In the 1952 group a few haematomata were encountered among the 160 stellate blocks performed; and it was thought prudent, in the 1954 group of patients who were given anticoagulants, to delay the first heparin injection for six hours. In addition xylocaine without adrenalin was used, to avoid bleeding from the reactive hyperaemia which must occur when the vaso-constrictive effect has worn off. Only one case of haematoma of the neck was encountered, and was not sufficiently troublesome to interfere with treatment.

TABLE IV

Results of Treatment

Year	*Number of patients*	*Recovered*	*Improved*	*Not improved*	*Died*	*Treatment*
1952	16	4	1	2	9	Repeated stellate block
1953	18	4	2	3	9	No specific treatment
1954	15	8	3	0	4	One stellate block and anticoagulants
1955	11	6	1	1	3	Anticoagulants alone
Total	60	22	7	6	25	..
Per cent.	100	37	12	10	41	..

Results

Assessment. It is generally agreed that, with few exceptions, most of the neurological recovery possible from cerebral embolism takes place in the first four weeks, and that very little change apart from that due to re-education and adaptation can be expected after three months. Certain workers, notably Leriche and Fontaine (1934), have held more optimistic views, but experience in this country seems less encouraging. The final assessment of results was therefore made by examination three months after the embolism, and the patients were divided into four groups: 'recovered', 'improved', 'not improved', and 'died'. Recovery meant that the patient noticed minimal or no disability, and was able to return to a normal life with full work. Some loss of fine-movement dexterity in the hand was considered compatible with 'recovery' if the above criteria were fulfilled. Probably all patients with initial complete hemiplegia continue to show permanent minimal pyramidal signs. 'Improved' meant that some useful movement was possible at the elbow and wrist. 'Not improved' indicated the group in which no return of arm movement occurred below the shoulder, although some leg function was regained. Almost all patients surviving embolic hemiplegia regain some movement of the shoulder and of the lower limb.

Analysis of Results

The results are shown in detail in Table IV, and are analysed as follows with regard to prognostic factors.

1. *Stellate block.* There was no appreciable difference in results between the 1952 group, who were treated by repeated stellate block, and the 1953 control group, who received no specific treatment. In each group four patients recovered and nine died. This suggests that, where the neurological disability is

due to distant and reversible vascular effects of the embolism, nothing permanent is to be gained by immediate reversal of these effects, however striking the immediate result. If this is true, any recovery after stellate block suggests that equal recovery might well occur without it. The difficulty is, of course, that in any particular case of acute complete hemiplegia there is no way of foretelling

TABLE V

Statistical Comparison of Results

Year	*Patients who recovered or were improved*	*Patients who died or were not improved*	*Total*	*Treatment*
1952 1953	11	23	34	Repeated stellate block or no specific treatment
1954 1955	18	8	26	One stellate block and anticoagulants, or anticoagulants alone
Total	29	31	60	

$P = 0{\cdot}025$.

The results in 1952 and 1953 were similar, as were those in 1954 and 1955.

its outcome at the beginning, when presumably treatment is going to be of most value. The following case histories illustrate this point, and also the danger of attributing recovery to treatment.

Case 9. A woman aged 49 years was admitted with a complete left hemianopia and some disturbance of sensation of the left arm; the onset had been sudden, the hemianopia had not spared the macula, and auricular fibrillation was present. A right stellate block was begun, and as the needle pierced the skin the patient said 'I can see better already'. The procedure was stopped, and within 15 minutes the visual fields were full. No doubt this would have been claimed as a therapeutic success if the injection had been done earlier.

Case 4. A man of 38 years was admitted in 1952 with a right hemiplegia due to an embolism from a fibrillating heart. He was treated with his first stellate block, which resulted in a complete Horner's syndrome, and he then began to move his arm a little and recover his speech. Not until the next day was it noticed that stellate block had been done on the side of the hemiplegia, instead of the side of the brain lesion.

2. *Anticoagulant treatment.* There was very little difference in outcome between the patients treated by stellate block and anticoagulants (1954) and those treated by anticoagulants alone (1955). Just over half recovered and just over a quarter died in each group; it seems, therefore, that the addition of a stellate block to anticoagulant therapy is of no advantage. If, however, the groups who received anticoagulants (1954 and 1955) are added together, and compared with the groups who did not (1952 and 1953), it will be seen that, of the 'anticoagulant' groups, 54 per cent. recovered and 26 per cent. died, whereas 23 per cent. recovered and 53 per cent. died in the other groups. As the numbers are small, statistical analysis of the above results does not give much help; but if the 'recovered' and 'improved' cases are added together, and the 'not improved' and 'died' similarly treated, it becomes plain that the control series and the

stellate block series give a very similar result, and the two anticoagulant series, with and without stellate block, give an equally similar but much more encouraging result. This is shown in Table V, and Fisher's exact method shows the probability (P) to be 0·025; the risk of the figures occurring by chance is one in 40, a result generally regarded as significant.

TABLE VI

Interval between Onset of Embolism and Treatment, in relation to Prognosis

	All cases					*Anticoagulant treatment*					*No anticoagulant treatment*				
Interval between stroke and treatment or (in control cases) admission	*Total*	*Recovery*	*Improvement*	*No improvement*	*Death*	*Total*	*Recovery*	*Improvement*	*No improvement*	*Death*	*Total*	*Recovery*	*Improvement*	*No improvement*	*Death*
Under 6 hrs.	20	9	2	1	8	8	6	1	0	1	12	3	1	1	7
6–12 hrs.	23	10	3	3	7	10	6	2	0	2	13	4	1	3	5
12–18 hrs.	10	2	1	1	6	6	2	0	1	3	4	0	1	0	3
18–24 hrs.	4	0	0	1	3	1	0	0	0	1	3	0	0	1	2
Over 24 hrs.	3	1	1	0	1	1	0	1	0	0	2	1	0	0	1
Total	60	22	7	6	25	26	14	4	1	7	34	8	3	5	18

3. *The intervals between stroke and treatment* were studied in the anticoagulant-treated groups, and are shown in Table VI. It will be seen that, in the whole series, 53 of the 60 patients were in hospital within 18 hours of the stroke, and, in the case of the 43 admitted within 12 hours, the 'recovered' or 'improved' patients numbered only five more than those who died or showed no improvement. Of the 18 patients, however, who received anticoagulant treatment and recovered or improved, 15 were treated within 12 hours. This might be thought significant if it were not seen that, in the groups not receiving anticoagulants, nine of the 11 patients who recovered or improved were admitted within 12 hours, and, although these were only one-third of the patients so admitted, it seems that any improvement among patients admitted early might be due to chance. Nevertheless, the recovery rate in the 'anticoagulant' group admitted within 12 hours suggests that early treatment is desirable.

4. *Severity and extent of the stroke, and age of the patient.* In analysing these prognostic factors only the 1953 and 1954 patients have been used, because of the similarity, even in detailed analysis, between the 1952 and 1953 groups and between the 1954 and 1955 groups. Tables VII and VIII show details of the two groups analysed, and it will be seen that they are reasonably comparable in the distribution and severity of the lesions. In the control group 12 of the 18 patients showed a complete loss of function initially, compared with 10 of the 15 patients who were treated. In the control series the natural history of events seems to depend on the age of the patient and the extent of the lesion.

In the control group nine patients died, and their average age was 57 years; six had a complete paralysis, and six had sensory loss. Of the nine who survived the average age was 43 years; six had a complete paralysis, but only three had sensory loss, and two of the latter showed no improvement. This result agrees with the general view that the older the patient, and the more widespread the

lesion, the worse the prognosis. In the treated group the four patients who died averaged 62 years of age, and three of them showed an extensive lesion with sensory loss. Only four of the 11 surviving patients (average age 42 years) had sensory loss; the prognostic criteria therefore still hold good in the treated group, and the only change is an overall improvement in results. It was encouraging to find that completeness of recovery was more than twice as

TABLE VII

Control Cases (1953)

Case number	*Sex*	*Age (years)*	*Side of body affected*	*Extent of lesion*	*Severity of lesion*	*Result*
17	F	30	L	Hemiparesis; face and arm worse than leg	Severe weakness	Improved; hand movements poor, and elbow weak
18	F	64	R	Hemiplegia and hemianaesthesia; aphasia	Complete	Death. Middle cerebral artery completely occluded
19	M	62	R	Hemiplegia; hemianaesthesia; aphasia. Blind L. eye	Complete	Death. Internal carotid artery occluded in carotid canal
20	M	46	L	Face and arm only affected	Moderate weakness	Full recovery
21	F	27	L	Face and arm; leg, slight weakness	Complete (face and arm)	Not improved
22	F	35	..	Aphasia only	Complete	Very good recovery
23	M	68	L	Hemiplegia; loss of position sense; hypalgesia	Complete	No improvement
24	F	59	L	Hemiplegia; hemianopia; hemianaesthesia	Almost complete	Death. No autopsy
25	F	47	R	Hemiplegia; aphasia; slight loss of pain sense	Incomplete; moderate weakness	Death after 8 weeks. Cerebral softening; no embolus found
26	M	64	R	Hemianopia only	Complete	Small quadrantic permanent defect
27	F	21	L	Hemiplegia; hemianopia; loss of position sense. Unconscious for 12 hrs.	Complete for 24 hrs.	Full recovery
28	M	69	R	Hemiplegia and hemianaesthesia; aphasia	Complete	Death. Embolus impacted in middle cerebral artery
29	F	32	L	Face and arm only	Moderate weakness	Full recovery
30	F	31	R	Hemiplegia and aphasia	Slight movement of leg	Death. No autopsy
31	F	67	L	Hemiplegia; hemianopia; hemianaesthesia	Complete	Death. No autopsy
32	M	45	L	Hemiplegia; sensory testing impossible	Complete	Death. Complete occlusion of middle cerebral artery
33	F	59	R	Hemiplegia; hemianalgesia; loss of position sense	Complete	Not improved
34	M	60	L	Hemiplegia; Jacksonian epilepsy	Complete	Death after 6 weeks. Cerebral softening; no embolus found

common in the treated group, and that five of these recoveries followed complete paralysis at the outset. An interesting point is the rate of improvement. Without treatment the patients who recovered completely seemed to get well rapidly, in steps rather than by degrees, and marked changes in movement and power were sometimes observed overnight. In the 'anticoagulant' groups, although this rapid improvement by steps was seen in some cases of complete recovery, about half of the patients who recovered showed a steadier curve of improvement. It is possible that these cases of smoother progression represent the prevention of thrombotic spread, so that such anastomotic channels as exist can play their part as the cerebral oedema subsides.

Conclusion

The results suggest that in the 1954 and 1955 groups of treated patients the natural history of cerebral embolism was significantly improved, although the main prognostic factors—the age of the patient and the extent and completeness of the lesion—remain relatively important. Even if this improvement is

recognized, at least two questions remain to be answered. First, is the improvement sufficient to warrant any risk involved in treatment? The risks have already been discussed, and it is probably unwise to subject elderly or hypertensive patients to them for the following reasons: (1) Capillary fragility is more pronounced in older people, and so the tendency to bleed, if the prothrombin time is long, is probably greater. (2) Old people stand haemorrhage into the

TABLE VIII

Patients treated with Anticoagulants and one Stellate Block (1954)

Case number	*Sex*	*Age (years)*	*Side of body affected*	*Extent of lesion*	*Severity of lesion*	*Result*
35	F	64	L	Hemiplegia; hemianopia; hemianaesthesia in all modalities	Complete	Improved; weakness of arm and hemianopia persist
36	F	65	L	Hemiplegia; hemianaesthesia; hemianopia	Complete	Death. Embolism of middle cerebral artery
37	M	59	L	Hemiplegia; slight movement of leg from the first	Almost complete	Death 6 weeks later. Cerebral softening
38	F	25	R	Hemiplegia; aphasia	Complete paralysis; partial aphasia	Recovery
39	F	64	R	Hemianopia only	Complete	Improved after stellate block. Permanent quadrantic defect
40	F	59	L	Face and arm only. No sensory loss	Complete	Recovery
41	M	32	R	Hemiparesis; some loss of position sense in hand	Incomplete	Recovery
42	M	61	L	Hemiparesis	Incomplete	Improved. Persistent weakness of hand and forearm; spasticity pronounced
43	F	68	R	Hemiplegia; aphasia; hemianaesthesia	Complete	Death. Embolism of middle cerebral artery. Haemorrhage in each renal pelvis
44	F	40	..	Aphasia only. No pyramidal signs	Complete	Recovery
45	F	21	L	Hemiparesis; loss of position sense	Incomplete	Recovery
46	M	41	R	Aphasia; hemiplegia; no sensory loss	Complete	Recovery
47	F	30	L	Hemiparesis; no sensory loss	Incomplete	Recovery
48	M	57	R	Hemiplegia; hemianaesthesia; aphasia	Complete	Death. Complete block of L. middle cerebral artery
49	F	32	L	Hemiplegia; hemianaesthesia; hemianopia	Complete	Recovery

renal system badly, and tend rapidly to develop renal failure if this occurs. (3) It is more difficult to control prothrombin time in older people, and diurnal variations with standard dosage are frequent and sometimes alarming, as was evident in Case 43 (see page 341). It is therefore suggested that for patients over the age of 65, or patients whose blood-pressure is above 190 systolic or 110 diastolic, the anticoagulant dose should be reduced to two-thirds of the routine amount, so that the prothrombin time does not exceed three times the normal at most; and it is also suggested that any undue lability in the readings should be a reason for stopping treatment. If these precautions are taken there seems, judging by the present series, to be no risk of bleeding, and no reason to suppose that anticoagulant therapy is dangerous in cerebral embolism.

The second question is whether stellate block is effective. The results of anticoagulant therapy without it were very similar to those obtained with the combined treatment, and suggest that stellate block is unnecessary. There is the added advantage that treatment with anticoagulants can begin at once when the patient has been admitted to hospital. The role of stellate block seems to be the relief of cerebral vasoconstriction following embolism, but the results suggest that this relief does not alter the ultimate prognosis. In addition, some

authorities do not believe that the sympathetic ganglia control intracerebral blood-flow, and others do not agree that reversible vasoconstriction can produce permanent damage, so that on many counts it seems justifiable to discard this procedure.

It is a pleasure to thank Dr. K. D. Keele and Dr. J. E. Royds for allowing me access to their patients suffering from cerebral embolism, and to thank Dr. W. Ritchie Russell for his comments and advice.

Summary

1. Sixty consecutive patients with cerebral embolism, out of a total of 575 cases of acute apoplexy, have been studied.

2. They were divided into four groups: (1) 1952: 16 patients treated by repeated stellate block; (2) 1953: 18 patients as controls; (3) 1954: 15 patients treated by one stellate block followed by 14 days of anticoagulants; (4) 1955: 11 patients treated by anticoagulants.

3. The dangers of anticoagulants in this condition are discussed, and present-day opinions reviewed. In the present series no ill effects were demonstrated in the infarcted area of brain at necropsy in fatal cases, but one elderly patient died of uraemia as a result of bilateral renal haemorrhage.

4. It is suggested that patients over 65 years of age, and patients with hypertension, should receive a modified course of anticoagulants.

5. The results have been analysed and tabulated, and show that at the end of three months (1) there was no significant difference between the control group of patients (1953) and the patients treated by repeated stellate block (1952); (2) there was no significant difference between the group of patients treated by anticoagulants and stellate block (1954) and those treated by anticoagulants alone (1955); (3) there was a significant difference between patients who had received anticoagulants (1954 and 1955) and those who had not (1952 and 1953), mortality being lower and the number of recoveries increased.

6. It appears that anticoagulant therapy, if properly and carefully given, is without danger and of advantage in treating cerebral embolism, and that stellate-ganglion block has no effect on the final outcome.

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A SUBACUTE PROGRESSIVE ENCEPHALOPATHY WITH MUTISM, HYPOKINESIA, RIGIDITY, AND MYOCLONUS[1]

A Clinical and Pathological Account of Three Cases

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With Plates 34 to 36

The so-called degenerative diseases of the nervous system form a complex miscellany due to a wide variety of agents. When one considers such diverse entities as hepato-lenticular degeneration, subacute combined degeneration of the spinal cord, and the various forms of peripheral neuropathy, it will be seen how little the histological peculiarities of the neural lesions help in interpreting these disorders or in establishing their cause. This is especially true of the neuronal loss seen in certain kinds of organic dementia. The description of an apparently new type of encephalopathy, with well-defined and unusual clinical features, may therefore contribute to our understanding of these conditions. Most cerebral degenerations run a course extending over many months or years. We here report three cases of a disease occurring in middle life, and ending fatally within a period of about three months. The illness was characterized by progressive personality change, hypokinesia, mutism, involuntary movements of myoclonic type, and the rapid development of decorticate rigidity. The electroencephalograms were abnormal, and possibly diagnostic. Necropsy revealed no evidence of neoplasm, encephalitis, or significant cerebro-vascular disease, but there was in each instance a diffuse but variable loss of neurones, affecting mainly the cortex and central grey matter, together with astroglial proliferation, at times intense, and a variable degree of status spongiosus. The white matter was intact.

A few similar case reports have been published, but the disorder is not generally known. This is surprising, as once encountered it is unlikely to be forgotten or to be confused with any other organic disease of the nervous system, the rate of progression, clinical features, and electroencephalographic findings all differing from those found in other forms of cerebral degeneration. Heidenhain (1928) described two patients in whom dementia, generalized rigidity without pyramidal signs, cortical blindness, and involuntary movements, similar to those exhibited by our patients, were the main symptoms of a rapidly progressive form of cerebral degeneration, coming on in middle life and ending fatally within 20 weeks. He also described a third patient in whom the

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disease was of much longer duration. Necropsy revealed a great loss of neurones, affecting in particular the most posterior parts of the brain, marked astrocytic proliferation, and variable status spongiosus. In 1930 Hallervorden reported a case with a similar pathological basis. The first detailed account of the condition is that of Alajouanine and van Bogaert (1950). Under the heading 'affection caracterisée par une contracture tétanoïde avec hypercinésies variables et à évolution subaiguë mortelle', they described two middle-aged patients who rapidly became demented, with decorticate posture and intense rigidity of the limbs. Involuntary movements of myoclonic type occurred, both spontaneously and in response to sensory stimulation. Both patients became mute, and almost totally incapable of voluntary movement, the authors attributing these findings to the extraordinary rigidity that had invaded the whole musculature. The first patient died within a month, the second within three months. In both instances the histological findings were slight when contrasted with the clinical features. There were small areas of cell loss in the deeper cortical layers and central grey matter, with diffuse astrogliosis, but no evidence could be found of demyelination or inflammatory reaction. Jones and Nevin (1954) later described two patients with a rapidly progressive cerebral degeneration. Mental disorder, focal neurological disturbances, and myoclonic epilepsy were the main symptoms. Both patients became completely mute, and the first at least exhibited a typical decorticate posture. Both died within 15 weeks. One of us (C. A. P.) had had the opportunity of seeing these two cases, which much resembled our own. Examination of the brain revealed a generalized loss of cortical neurones, marked glial overgrowth, status spongiosus of the cortex, and, in one of the cases, acute softenings in the basal ganglia. A vascular aetiology was inferred, although, as the authors point out, the pathological findings were not those typical of cerebral arteriosclerosis. More recently McMenemey and Nevin (1955) have described five further patients (their report includes a very brief description of Case 1 of the present series). Our three cases have formed the basis of preliminary communications to the Royal Society of Medicine (Spillane and McMenemey, 1956) and to the Society of Physicians in Wales (Pallis, 1956).

Case Reports

Case 1. A woman aged 53 years. Fatal illness lasting 10 weeks. Insidious onset of personality change, followed by disturbance of speech, stiffness of the right arm and leg, generalized rigidity, and 'myoclonus'. Hypokinesia. Mutism. Decorticate posture. Trismus. Fluctuating bilateral pyramidal signs. Retention of urine. Low-grade fever throughout, with terminal hyperpyrexia.

Early in December 1953, V. B., a housewife of 53 years, became tired, listless, and apathetic. There had been no previous illnesses of note, and there was no family history of dementia. Her family attributed her symptoms to worry. She became depressed, and began to express fears of insanity. Although there were no definite somatic complaints, she took to bed in the middle of December. She became increasingly reluctant to speak, although what little speech she would utter would be apposite and adequately articulated. She gradually lapsed into monosyllables, and then into a state of complete mutism,

which rendered the further evolution of her mental state difficult to assess. Shortly after taking to bed she noticed awkwardness of the right hand. It became stiff and clumsy, and she refrained from using it while eating. By the end of the month she was holding the fist clenched and the right arm tightly pressed against the body. During her short periods out of bed she would drag the right leg. 'Twitching' of the right arm was noted on 30.12.53. She was admitted to St. David's Hospital, where she was seen by one of us (J. D. S.), and transferred to the Neurological Department, Cardiff Royal Infirmary, on 6.1.54.

Examination. A well-covered middle-aged woman, she lay on her back, her head turned to the left. A generalized rigidity pervaded the whole musculature. The arms were tightly adducted at the shoulders, the elbows flexed, the forearms pronated, and the fists clenched. The lower limbs were extended. The neck was held stiffly. She would maintain this posture for many hours at a time. She appeared to see, her eyes following the examiner about. She would respond to painful stimuli, and would obey simple instructions such as 'shut your eyes' and 'put out your tongue', but not more complicated ones. She was totally mute, and appeared incapable of initiating any kind of voluntary movement, such as turning about in bed. She could chew and swallow, but made no attempt at feeding herself. There was continued retention of urine, requiring regular catheterization.

The fundi were normal. The pupils were dilated, but reacted briskly to light. She could not co-operate in a formal examination. There was no obvious facial weakness. She showed marked pouting and sucking reflexes, a whole series of protrusor spasms of the lips following any kind of contact. A grasp-reflex could be elicited in the right hand. The disturbance of tone was throughout her illness most marked on the right side. The tendon-reflexes were bilaterally brisk, with slight clonus at the right knee and ankle. The plantar response was probably extensor on the right, and equivocal on the left. Tonic neck-reflexes could not be demonstrated. From time to time her head would jerk to the left four or five times in rapid succession. Twitching movements of the mouth were frequent, and sustained deviation of the eyes, in one or other direction, would be observed. Occasionally the right upper limb would give a sudden jerk. Although many muscle-groups were affected, the rigidity prevented much displacement.

She had no fever on admission. The pulse was regular, the rate 100 per minute, and the blood-pressure 150/95. The radial arteries were not palpably thickened. Examination of the heart, lungs, and abdomen revealed nothing abnormal. A faint macular rash was seen over the front of the chest and outer aspects of both arms. It did not persist.

Progress. Her condition deteriorated steadily during the next four weeks. She remained totally mute. A few days after admission she developed trismus, and had to be fed by nasal tube. The tone in the flexors of the neck was now such that her head would remain in the air when her pillows were withdrawn. The involuntary movements increased in amplitude and frequency. There would be chewing movements, punctuated by bursts of spasmodic pouting, repetitive elevation of one or both eyebrows, and brief oculogyric spasms. 'Palatal myoclonus' was not observed. Most of the time her fists would be tightly clenched and held close against her chin (Plate 34, Fig. 4). On occasions the pectoral muscles would contract clonically, and she would then punch herself on the jaw. These movements were usually unilateral, but at times both sides would be affected simultaneously. The deltoids would occasionally be involved, and the alternating movements at the shoulders would then grotesquely caricature a person playing an accordion. The involuntary movements showed no definite periodicity. They would break out in rapid sequence,

usually in groups of six or eight, but at times continued unabated for several minutes. Their onset would be quite explosive if she was disturbed by tactile, auditory, or visual (flash) stimuli. The movements never progressed to a frank grand mal attack. Synchronous flexion of both forearms (either spontaneously or in response to sensory stimulation), typical of the myoclonus of epileptics, was never observed. The lower limbs were not involved. The movements lessened during sleep, but did not cease altogether. From time to time a fine rapid tremor affected the right hand and forearm.

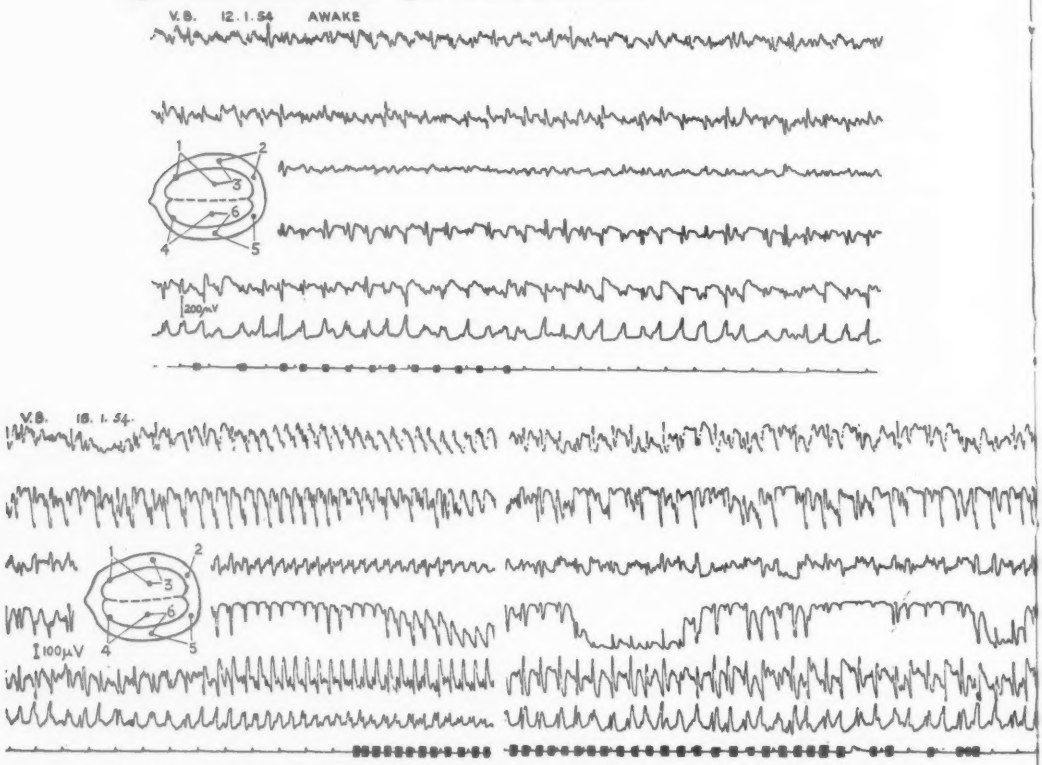

FIG. 1. Case 1. *Top*: Electroencephalogram in the fourth week of illness. The record is asymmetrical. Delta waves and continuous high-voltage slow spikes occur in all leads from the left hemisphere. The spikes are focal in the left fronto-temporal region. *Bottom*: Six days later. The slow spikes and waves have become generalized. Neither record is affected by the occurrence of involuntary movements, indicated by black squares on the time-trace.

Although not unconscious, she was completely helpless and utterly incapable of any voluntary act. Until the end she appeared to appreciate painful stimuli on both sides of the body. Pyramidal signs were never much in evidence, the plantar responses being inconstantly extensor on one or the other side. No papilloedema developed, and as far as could be ascertained she had not become blind. She did not appear in pain, and never vomited. She continued to have retention of urine and faeces. A mild fever, rarely exceeding 100° F., persisted. Hypostatic pneumonia eventually developed, and she died after 24 hours of hyperpyrexia, the last recorded temperature being 107° F.

Investigations. On admission the total white blood count was 8,500 per c.mm., with a normal differential count, and haemoglobin 14·4 gm. per 100 ml. The urine contained a trace of albumin, two or three leucocytes per high-power field, and much urobilinogen, but no porphyrins. The blood-urea was 60 mg. per 100 ml. The serum contained sodium 135 mEq., potassium 4·1 mEq., chloride 94 mEq., and bicarbonate 23 mEq. per litre. The blood Wassermann and Kahn tests were negative. The fasting blood-sugar was 112 mg. per 100 ml.

Radiographs of the skull and chest, and a left carotid angiogram, were normal. An air encephalogram, performed during the first week in hospital, showed an excess of air over the cerebral convexities, especially on the left. The cerebrospinal fluid was examined several times. The pressure never exceeded 140 mm. of fluid. The protein-content varied from 23 mg. per 100 ml. (on 8.1.54) to 100 mg. per 100 ml. (on 19.1.54). The cell count never exceeded three per c.mm. The Lange curve on 1.2.54, five days before the patient died, was 1111100000.

Electroencephalograms. Serial recordings were made which showed a progressive deterioration of unusual type. On 12.1.54 the record (Fig. 1, top) was markedly asymmetrical, delta waves and continuous high-voltage slow spikes appearing diffusely in all leads from the left hemisphere. There was no alpha rhythm. The spikes were focal in the left frontotemporal region. The abnormal activity was also visible, but at a much lower potential, in the leads from the right hemisphere. A series of involuntary movements of the right upper limb, at a frequency of about one per second, was not associated with any change in the appearance of the record. On 18.1.54 generalized slow-spike-and-wave complexes were seen (Fig. 1, bottom), arising almost symmetrically from both hemispheres, at an amplitude at times exceeding 300 μV. and at a frequency of about two per second. Bursts of generalized involuntary movements occurred during the recording but, although the individual movements appeared to coincide with each of the wave-and-spike complexes, the record itself was remarkably uniform, whether movements were present or not. No attempt was made to determine the effect of sleep or of various drugs on the electroencephalogram.

Case 2. A woman aged 51 years. Fatal illness lasting 11 weeks. 'Myoclonic' movements of the left arm, later affecting both upper limbs and trunk. Insidiously developing mutism, periodic at first. Recurrent grand mal, with prolonged periods of post-ictal stupor. Organic confusional syndrome. Hypokinesia. Late development of decorticate posture. Biochemical evidence of disturbed liver function.

M. L., an unmarried nursing sister aged 51 years, was admitted to St. Woolos Hospital, Newport, on 17.12.54, and transferred the same day to the Neurosurgical Unit at the Cardiff Royal Infirmary, under the care of Mr. Charles Langmaid. Towards the end of October 1954 she had had a short feverish illness, with cough, headache, and a running nose. A week later she became aware of sudden jerking movements of the left arm. These were of considerable amplitude but infrequent, single spasms occurring at intervals of several days. There was some recurrence of headache. In the middle of November she was well enough to visit friends in Huddersfield, but returned feeling depressed. On the evening of 3.12.54 she was found alone at home, on the floor, face downwards, by her brother on his return from work. She did not regain her senses until the next afternoon. During this period of stupor, lasting about 24 hours, 'shock-like' twitches were observed, usually in groups of two or three, affecting both arms and 'pulling them across the chest'. There was no undue mental confusion

on recovery. She remained in bed the next two weeks. Her speech gradually became scanty, 'awkward', and slow. At times she would be unable to sustain a conversation, and would stop in the middle of a sentence and stare into space, or would seem puzzled when spoken to and fail to answer. On other occasions she would speak volubly and appeared agitated. During the next few days she again complained of slight generalized headache. The involuntary movements became more frequent, now affecting both arms, singly or simultaneously, the trunk, and the lower limbs. The jerking of the arms would be quite violent, and at times interfered with her feeding herself. On one occasion a sudden movement 'shot a tray she was holding across the room'. On another occasion, when going to the toilet, the trunk suddenly flexed and she was thrown to the ground. On 10.12.54 she 'slept the whole day', and was difficult to rouse. She improved the next day. By 16.12.54 she would answer only 'yes' and 'no' to questions, and not always appropriately. On 17.12.54 she was found unconscious in her room, and was admitted to hospital. There was no previous history of epileptic disturbance, and no family history of epilepsy or dementia. She had suffered from mild jaundice three years previously, presumed to be infective hepatitis. There had been no complications.

Examination (21.12.54) revealed a thin, middle-aged woman, with no fever, showing signs of recent loss of weight. No abnormalities were found in the heart, lungs, or abdomen. The blood-pressure was 150/90. There was no peripheral arteriosclerosis. There was no icterus, clubbing, or palmar erythema, and no spider naevi were seen. She was sitting up in bed, agitated and restless. Far from being mute, she was garrulous, her speech being irrelevant and at times incoherent. There was no dysarthria. It was not possible to conduct any rational conversation with her. She repeatedly had to be restrained from getting out of bed. She was incontinent of urine and faeces.

She would not co-operate in a neurological examination, but there did not appear to be any paresis or ataxia of the limbs. She was very tremulous on attempting to feed herself or to pick anything up. A slight diffuse rigidity was noted, predominating in the lower limbs, which were usually held in extension. There was no stiffness of the neck. From time to time one or other shoulder, or both, would suddenly jerk upward. No twitching in the peripheral muscle-groups was observed at this stage. There was no papilloedema. The pupils were large, but reacted briskly to light. The jaw-jerk was exaggerated. There was no facial weakness, but she showed marked reflex pouting. Swallowing was not affected. The tendon-reflexes were symmetrically sluggish in the arms, but the knee- and ankle-jerks were brisk. The plantar responses were equivocal. No tonic neck-reflexes could be elicited, and there was no reflex grasping. Formal sensory testing was not possible.

Progress. Her condition deteriorated in an irregular manner until her death a month later. She had three major convulsions during this period. The immediate onset of only one of these attacks was actually witnessed. No prodromal myoclonus was observed. No focal features were noted during these episodes, and there were no focal sequelae. Each fit was followed by prolonged post-ictal stupor, lasting up to 36 hours. General deterioration was obvious after each attack. The agitated state observed on admission gave way to one of apathy and total mutism. She yawned frequently. At first the limbs were not held predominantly in any one position. She eventually developed a decorticate posture, with the legs extended and the upper limbs firmly adducted and flexed. She maintained this posture during the last two weeks of her illness, except during the episodes of post-ictal stupor, when the hypertonus occasionally, but not invariably, subsided and she would become limp, with loss of her reflexes.

The involuntary movements increased considerably as her condition progressed. Any unexpected stimulus, tactile, auditory, or visual, would provoke a 'startle reaction', consisting of one or more sudden flexion-spasms of head and trunk with elevation of the shoulders and further adduction of the arms. Stimuli would then be without effect for the next few minutes. During the last fortnight sudden synchronous spontaneous flexion movements of the forearms were seen. These were usually single, but occasionally occurred in small 'runs' of three or

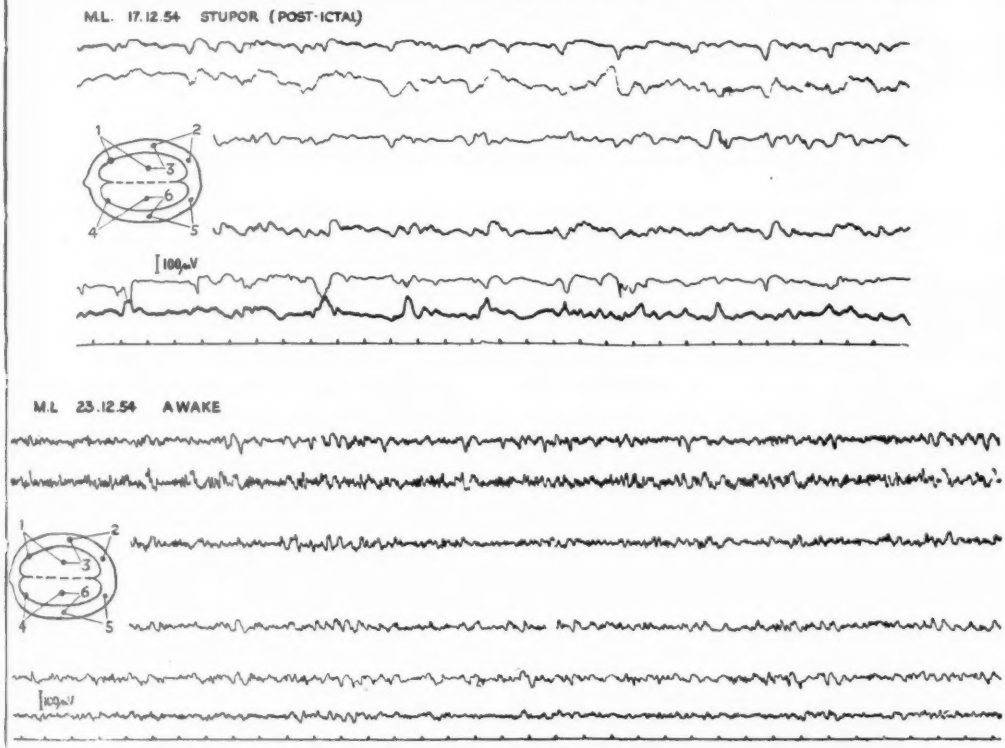

FIG. 2. Case 2. *Top*: Electroencephalogram in the seventh week of illness. Post-ictal stupor. Bilateral delta and sub-delta rhythms interrupted, particularly in leads from the left hemisphere, by 'periodic' high-voltage slow waves. *Bottom*: six days later. The patient has recovered from stupor. Some alpha rhythm is now present, together with much bilateral theta and delta activity.

four. They never became generalized. Although at various times one or both plantar responses were found to be equivocal, probably extensor, pyramidal signs were never very definite, and clonus was never observed. The fundi remained normal, and as far as could be ascertained vision was retained throughout. She remained without fever except in the periods of post-ictal stupor, when the temperature would reach 101° F. The fever would subside as she recovered consciousness after each attack. She never vomited. She remained incontinent throughout her illness.

Investigations. Radiographs of the skull and chest were normal. Contrast studies were not performed. The white blood-cells were 6,800 per c.mm., with a normal differential count, and haemoglobin 94 per cent. The blood Wassermann

and Kahn reactions were negative. The blood-urea was 24 mg. per 100 ml., and the fasting blood-sugar 104 mg. and 126 mg. per 100 ml. The serum contained sodium 135 mEq., potassium 4·6 mEq., chloride 91 mEq., and bicarbonate 28 mEq., per litre. The total serum-protein was 7·6 gm. (albumin 4·6 gm.) per 100 ml., alkaline phosphatase 7·5 King–Armstrong units per 100 ml., serum-bilirubin 0·4 mg. per 100 ml., thymol turbidity 9 units (normal 0 to 4), and zinc turbidity 19 units (normal 2 to 8). The urine contained no albumin, bile, or excess of urobilinogen. Chromatography failed to reveal any abnormal amino-aciduria.

Several examinations of the cerebrospinal fluid were made. The pressure never exceeded 130 mm. of fluid. The protein-content was variable, being recorded as 160, 62, 94, and 76 mg. per 100 ml., at approximately weekly intervals. The cell count never exceeded three per c.mm. In the last specimen obtained the Lange reading was 1111220000. The earlier readings were 1111100000.

Electroencephalograms. The initial record (Fig. 2, top) was taken on 17.12.54, during one of the first episodes of post-ictal stupor, and was undoubtedly much influenced by this circumstance. No alpha rhythm was visible. The dominant activity consisted of slow bilateral delta and sub-delta waves of moderate voltage. Approximately every three seconds very slow waves of large amplitude occurred in all leads, but more particularly from the left hemisphere. This periodicity persisted throughout the recording. A further record (Fig. 2, bottom) was taken on 22.12.54, when she had recovered consciousness. There was now some normally responsive alpha rhythm at nine to ten cycles per second in the occipital leads, and in addition intermittent generalized theta and delta waves, much increased by overbreathing. On this occasion periodicity was not a feature.

Case 3. A woman aged 45. Mitral stenosis. Fatal illness lasting 18 weeks. Progressive dementia. Bilateral 'myoclonic' movements. Trismus. Mutism. Hypokinesia. Decorticate posture. Transient pyramidal signs. Detailed electro-encephalographic study.

In the middle of June 1955, M. H., a housewife of 45 years, began to lose sleep. She would pace up and down her room until 3 or 4 a.m. She became depressed, querulous, and occasionally incontinent of urine. There was no previous history of mental disorder, and no family history of dementia. She was taken on a holiday, but lost all interest in her food and her surroundings, and had to be brought home. She had difficulty in finding her words, and at times failed to recognize objects. On one occasion she said she could not understand what she had been reading in a newspaper. She was admitted to St. Cadoc's Psychiatric Hospital on 22.7.55, where she was found to be demented. The speech was slurred, the tendon-reflexes in the right arm and leg exaggerated, and the plantar response on the right suspect. There was mitral stenosis, and a left-sided pleural effusion. She was transferred to the Neurosurgical Unit, Cardiff Royal Infirmary, under the care of Mr. Charles Langmaid, on 2.8.55.

She was retarded, and there was marked poverty of speech. She said, 'How are you?' when formally greeted, but these were the only words she was heard to utter during her whole stay in hospital. She would sit up in bed and look around as if lost. When asked to write she took hold of the pencil, but could write nothing. She obeyed simple instructions, but tended to perseverate. The fundi were normal. There was no paresis of the limbs. Tone was considered to be increased on the right side. The reflexes were symmetrically brisk, the left

plantar response probably extensor, and the right equivocal. She was stated to 'respond to pin-prick by jerking movements', and at this stage a history was obtained of occasional twitching of the limbs during the previous fortnight. After bilateral carotid angiography (which revealed no evidence of an expanding lesion) she began to have fever, up to 101° F., which persisted for several days. She was transferred to the Medical Unit, under the care of Professor Harold Scarborough. She was first seen by one of us (J. D. S.) on 16.8.55, and mutism, decorticate posture, and involuntary movements mainly affecting the face and arms were noted. A month later there was an increase of tone in the flexors of the neck, and moderate adductor and flexor rigidity in the upper limbs, usually predominating on the right side. The trunk was slightly flexed, and the lower limbs adducted and rigidly extended. It was difficult to judge how much of her surroundings she appreciated. At times her gaze would follow the examiner, but for long periods she would remain with her eyes open, staring at the ceiling. She did not appear to understand orders, but reacted to noise by sudden flexion movements of the whole body. When the abdomen and legs were exposed for examination she made no effort to cover herself. She was never once observed to change her position in bed, to move her head on the pillow, to smooth out a sheet, or to reach for food or drink. She did not even attempt these acts. Had she done so, the rigidity was not such as to have prevented all movement. She would slowly chew and swallow food put in her mouth. She did not appear to recognize her relatives or medical attendants. She was incontinent of urine, but extremely constipated.

The fundi were normal, the pupils were dilated but reactive, and there was slight trismus. The right side of the face appeared flatter than the left. Testing of the reflexes was difficult on account of the disturbance of tone and of the ease with which generalized flexion-spasms were induced. In the upper limbs the reflexes were brisker on the right. No abdominal or plantar reflexes could be obtained. Spontaneous jerking movements affected the shoulders and, to a lesser degree, the flexors of the forearms. These movements were usually unilateral, and would occur as single jerks or as small runs of two or three movements, or as sequences lasting from 10 to 20 seconds, during which perhaps a dozen spasms would be noted. Facial twitching was frequent, and nearly always bilateral, affecting both upper and lower parts of the face. On this variable background of spontaneous involuntary activity other, more ample, movements were seen, precipitated by any sudden disturbance (auditory, visual, or tactile), and consisting of two or three widespread spasms, in which the flexors of neck, arms, trunk, and hips, and the adductors of the shoulders, would participate in various combinations (Plate 34, Fig. 5). Sudden sounds, provided they were adequately interspaced, would invariably bring on these major movements, but if the auditory stimuli were repeated at intervals of less than a minute there might be no response.

Progress. The decorticate posture was rigidly maintained as the weeks went by. The fists were held so tightly clenched that her palms were damaged by the impressed fingers. Contractures developed, and she seemed to experience pain when attempts were made to open her hands. Vision was probably retained to the end, as she continued to respond by a 'startle-reaction' to visual threats. Retention of urine became troublesome. During sleep the movements ceased and the rigidity of the limbs lessened somewhat, but the characteristic posture was usually maintained. No unequivocal pyramidal signs developed, and the fundi remained normal. She had no fever during the major part of her illness. Before death her temperature rose to 100° F. Although her condition had been slowly deteriorating for some time, a fair state of nutrition had been maintained,

and she had escaped bedsores and bronchopneumonia. Her rather sudden exitus was unexpected.

Investigations. Radiographs of the skull were normal. The chest films showed a cardiac configuration in keeping with mitral stenosis. On her admission there was radiological evidence of fluid in the left pleural cavity, but a month later the effusion had been absorbed. The Wassermann and Kahn reactions were negative. The white blood-cells were 8,200 per c.mm., with a normal differential count,

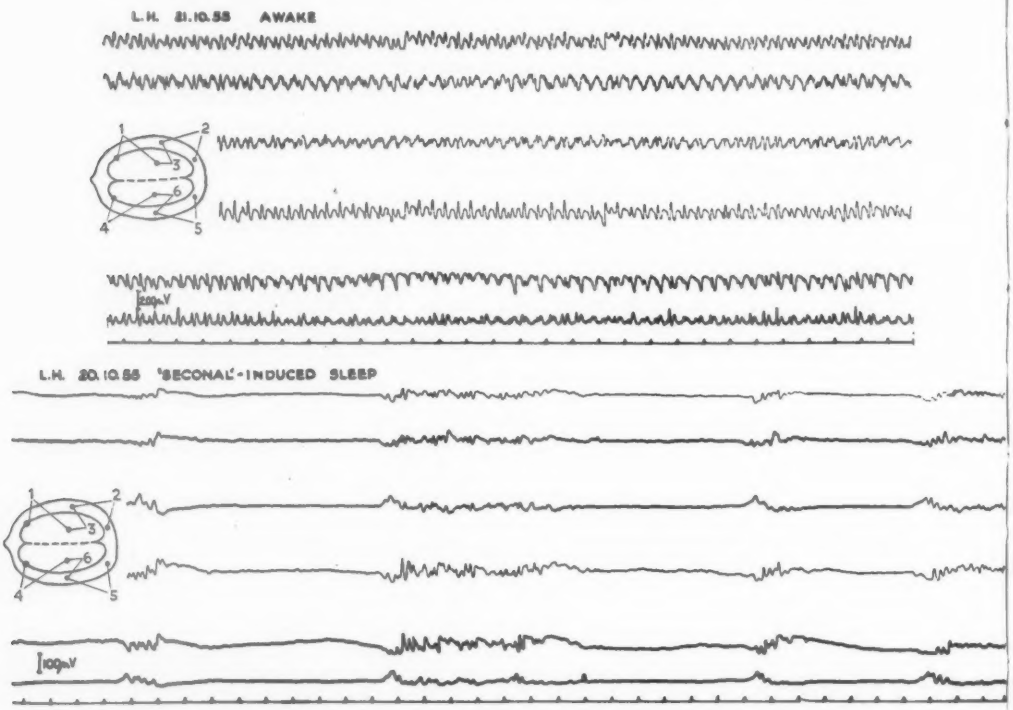

FIG. 3. Case 3. *Top*: Electroencephalogram in the 17th week of illness. Continuous, high-voltage, bilateral slow-spike and slow-wave complexes, with frontal predominance. This activity had been present from an early stage of the illness, and was not influenced by the occurrence of involuntary movements. *Bottom*: Seconal-induced sleep. Characteristic 'suppression-burst' activity. This record was taken on the day *preceding* the record illustrated at the top of this figure.

haemoglobin 13·4 gm. per 100 ml., and erythrocyte sedimentation rate (Wintrobe) 24 mm. in one hour. Blood cultures remained sterile after three weeks' incubation. The serum-protein was 7·7 gm. (albumin 4·9 gm.) per 100 ml. The urine contained neither albumin nor sugar, and nothing abnormal was found on microscopy.

Several examinations of the cerebrospinal fluid were made. The pressure never rose above 160 mm. of fluid. The cell count never exceeded three per c.mm. The protein-content was variable, ranging from 46 to 87 mg. per 100 ml. In the last specimen obtained, 12 days before the patient died, the Lange reading was 1111211000. Earlier it had been 1111100000.

Electroencephalograms were recorded at regular intervals. Some very unusual

patterns were observed. Shortly after admission the waking record, uninfluenced by drugs, showed almost continuous slow-spike-and-slow-wave complexes, of high voltage, occurring synchronously in all leads, at a rate of about two per second. This activity was symmetrical, although showing some frontal predominance. It persisted in a remarkably constant manner throughout her illness (Fig. 3, top) and was uninfluenced by the occurrence of involuntary movements, often seen during the recordings, or by various forms of sensory stimulation (flashes, sudden sounds, pin-prick, and sudden mobilization of the wrists).

The effect of certain drugs on the electroencephalogram was investigated. Intervals of at least three days were allowed to elapse between the administration of each drug, the record being allowed to revert on each occasion to its original pattern before the next test was made. The patient was awake during each of these recordings. *Epanutin* (sodium diphenyl hydantoin)—in a dose of 1 gm.—and *milontin* (*N*-methyl-α-phenylsuccinimide)—in a dose of 4 gm.—had similar effects on the record. The alternating high-voltage slow-spike-and-slow-wave complexes at two per second were replaced by long periods of irregular, generalized, slow theta activity at four to six cycles per second. Any sudden noise or painful stimulus would cause all electrical activity to 'flatten' for two or three seconds. This would be followed by the gradual reappearance of slow waves, at first periodic at intervals of 1·5 second, but gradually speeding up to revert eventually, after a period of about 15 seconds, to the pre-existing theta rhythm. *Tridione* (troxidone) in a dose of 3 gm. produced a similar alteration in the record, but sensory stimulation failed to produce the phase of inhibition observed in the recordings taken under the influence of epanutin and milontin.

The alteration of the record occurring under the influence of sleep (induced by seconal, 4½ grains) was extraordinary (Fig. 3, bottom). The record was completely different from all the previous ones. Intermittent bursts of activity at three to six cycles per second would be seen in all leads, lasting from one to eight seconds, followed by periods of absence of all activity persisting for up to 12 seconds. Various forms of sensory stimulation did not influence this periodicity. Although the test was performed late in the course of the patient's illness (nine days before her death), it was clear that these findings were directly attributable to seconal-induced sleep, and not to progression of the disease, for by the following day the electroencephalogram had reverted to its basic pattern (Fig. 3, top). It was unfortunately not possible to determine the effect on the electroencephalogram of natural sleep. On the two occasions when this was attempted the patient awoke during the placing of the electrodes.

Pathological findings

A complete necropsy was possible only in Case 2, but all three brains were available for study. They had been removed within 12 hours of death and fixed in formol-saline. Blocks were taken from the frontal, central, temporal, parietal, and occipital cortices, from many areas of white matter, and from the basal ganglia, pons, medulla, and cerebellum. They were embedded in paraffin-wax and celloidin, and the sections stained with haematoxylin-eosin, van Gieson, Nissl, phospho-tungstic-acid-haematoxylin, Heidenhain, Loyez, and Holzer stains. Frozen sections were also stained with Bielschowsky, Cajal, Scharlach R,

and Hortega stains (for both astrocytes and microglia). The following report of the three cases is based on Dr. W. H. McMenemey's unpublished communication to the Royal Society of Medicine on June 2, 1956.

Case 1. Externally the brain appeared normal. The posterior half had been cut horizontally to disclose a subcortical haemorrhage (considered terminal), 3 cm. by 3 cm. in size, in the right temporo-occipital area. The basal arteries did not show any significant arteriosclerosis. The meninges looked normal.

Cerebral cortex. Histological changes were most apparent in the occipital lobes (where area 17 showed no selective vulnerability), and least definite in the insula and posterior part of the frontal lobe. In the temporal convolutions the disease was intermediate in severity. There was a considerable proliferation of astroglia in all cortical layers. Lipoid granules were present in the cytoplasm of some of these cells, which in silver preparations were shown to have abundant fibrous processes and healthy-looking attachments to vessel walls (Plate 35, Fig. 6). This glial proliferation tended to mask a great loss of nerve-cells (Plate 35, Fig. 7). Most of the remaining neurones were healthy, and in Bielschowsky preparations exhibited intact axons, perhaps thinner than normal, and well-developed neurofibrils; but some had lost their nucleoli, so that their distinction from astrocytes was difficult. The cortex retained a distinct semblance of lamination. Microglial cells showed some activity, and in Scharlach-R preparations occasional 'gitter cells' were seen, suggesting active tissue-destruction. Sudanophilic fat was present in histiocytes, around blood-vessels, and in the cytoplasm of many nerve-cells. Status spongiosus was minimal: occasionally a nerve-cell was noticed lying stretched over a small 'bubble' in the ground-substance; we should have regarded such findings as due to artefact if we had not been looking for early manifestations of status spongiosus.

Central grey matter, brain-stem, and cerebellum. In the caudate nuclei there was a slight loss of nerve-cells, both large and small, with astroglial proliferation. In some of the larger surviving neurones the cytoplasm was vacuolated, and the nuclear membrane poorly defined. Similar changes, but rather more marked, were present in the lenticular nuclei and thalami. In the granular layer of the cerebellum there was patchy focal oedema around the blood-vessels, and an apparent increase in capillary vessels in the molecular layer. The Bergmann cell-layer was much spread out, and corpora amylacea were seen here and in the molecular layer, where there were also occasional aggregates of histiocytes resembling foci of necrosis. In the dentate nuclei there were many very pale cells of 'ghost-like' appearance.

In no part of this brain could there be found evidence of arterial or arteriolar disease. There were no features of inflammation. Inclusion bodies were not seen. The white matter appeared normal.

Summary. There was loss of nerve-cells in the cerebral cortex (greatest in the occipital lobes) and basal ganglia, with dense astrogliosis which was possibly reactive, and a slight degree of status spongiosus. Slight neuronal degeneration was found in the dentate nucleus. There was a terminal subcortical haemorrhage.

Case 2. A full necropsy was performed. In the liver, normal to the naked eye, small-cell infiltrations in the portal tracts were occasionally to be seen. The portal vein was free of thrombus. There was no evidence of disease except in the nervous system. Externally the brain appeared normal, and the cut surface

did not disclose any unusual features. The basal vessels were not thickened. The meninges looked normal.

Cerebral cortex. The changes were inconspicuous. There was slight astroglial proliferation in all areas, affecting mainly the outer layers, and most definite in the occipital region. Loss of nerve-cells was also slight: some 'ghost-like' forms were seen, suggesting cells in the process of disappearing. There was no status spongiosus.

Central grey matter, brain-stem, and cerebellum. In the caudate nucleus satellitosis was in excess of normal. Astrocytes, often containing lipoid granules in their cytoplasm, were increased in numbers. Occasional active microglial cells were noted. Fat, both free and in histiocytes, was seen around some of the vessels. There was a small focus of degeneration in the pons, just below the facial nucleus on the left side. It consisted of an aggregate of lymphocytes and histiocytes. In the cerebellum sudanophilic fat was noted around the vessels in the granular layer. There were occasional pale nerve-cells in the dentate nucleus.

The blood-vessels were everywhere normal. Three instances of partial cuffing of small veins were seen among the many sections carefully examined. Inclusion bodies were not found. The white matter was normal.

Summary. There was slight loss of neurones in the cortex (mainly occipital), with astrogliosis, and a focus of degeneration in the brain-stem. No status spongiosus was seen.

Case 3. This brain differed from those previously described in that it appeared atrophied to the naked eye, particularly in the temporal and occipital regions. The cut surface showed punctuation of the white matter in its more peripheral parts, and there was a small transventricular adhesion in the left lateral horn. The basal vessels and meninges appeared normal.

Cerebral cortex. There were several depressed glial scars on the surface of the convolutions (Plate 35, Fig. 8). These appeared to be of long standing, and to have antedated the recent illness. Patches of perivascular gliosis were seen in the occipital lobe, in the inferior temporal gyrus, in the hippocampus, and in Ammon's horn. There was marked astrogliosis in the occipital and temporal cortex and insula, extending throughout all layers, but greatest in layers 4 and 5. Loss of nerve-cells was considerable in these areas. There was fat in the macrophages and about the blood-vessels in all regions. A patchy status spongiosus was present (Plates 35 and 36, Figs. 8 and 9), but its distribution did not appear to bear any direct relationship to the degree of cell-loss or gliosis. It mainly affected layers 2 and 3, and in some regions was unusually focal in distribution. Healthy-looking nerve-cells were often seen in relation to these confluent spaces, which appeared to contain oedema fluid.

Central grey matter, brain-stem, and cerebellum. The changes were diffuse, consisting of loss of cells, fat in histiocytes, and astroglial proliferation (Plate 36, Fig. 10). In the pons there was a solitary instance of neuronophagia, in the accessory facial nucleus. In the medulla some of the cells of the olives were unduly pale. In the fasciculus gracilis there were a few aggregates of microglia. In the cerebellum there was patchy but intense gliosis of the molecular layer, and some loss of Purkinje cells. A little fat was to be seen in macrophages round the vessels of the granular layer. In the dentate nuclei there was a moderate loss of neurones, and some of the cells were very pale, indistinct, and had rather conspicuous spiky processes (Plate 36, Fig. 11). There was also a slight increase of glial cells (Plate 36, Fig. 12).

The white matter and blood-vessels appeared altogether normal, and there was no cuffing. No inclusion bodies were seen.

Summary. There was loss of nerve-cells in the cortex, basal ganglia, and dentate nuclei, considerable cortical astrogliosis, and status spongiosus. Depressed cortical scars were seen, and a few foci of perivascular gliosis. The changes in this brain were more pronounced than in the other two.

Discussion

I. *The aetiology* is unknown. No familial cases have been reported, and genetic predisposition does not appear to be of importance. The sexes are affected about equally. The 11 previously mentioned patients were aged 55, 53, 60, 61, 62, 66, 62, 57, 68, 53, and 57 years respectively, at the onset of the disease. All but three were in good health before their terminal illness. In Case 1 of McMenemey and Nevin (1955) the patient had had a left temporal meningioma removed 14 months previously. Their second patient had had an operation for otogenic cerebral abscess 20 months earlier, and their third patient had sustained a severe head injury, resulting in hemiplegia, two years before the illness. Surgical or accidental trauma is not recorded in any of the other cases. Heidenhain's (1928) second patient died of terminal septicaemia, and Hallervorden's (1930) patient of erysipelas. One of our patients had mitral stenosis, and during her last illness developed a pleural effusion, but there was no evidence of bacterial endocarditis. Another of our patients had been jaundiced three years previously, and showed abnormal flocculation reactions in the serum. At necropsy there was neither cirrhosis nor portal thrombosis. Cerebro-vascular disease, as ordinarily understood, was probably not a factor of much significance in any of the recorded patients. Although the available clinical data are rather scanty, nearly all the necropsy reports comment on the structural integrity of the major cerebral blood-vessels.

The disease is invariably fatal. In the 11 previously reported cases its duration varied from 12 to 20 weeks. Evidence of coincident nutritional or metabolic disorder, or of intoxication, has always been lacking. Although well-established ideas about infections of the nervous system have had to be altered since the recognition of subacute inclusion encephalitis, the general features of the illness do not suggest an infection. None of the well-known forms of primary cerebral degeneration, senile or presenile, progress at such a rate or in so inexorable a manner. Clinical analysis, it will be seen, has little to contribute to any discussion of aetiology. It will be pointed out later, however, that such an analysis may help to unravel the complex functional disorder which appears to be so characteristic a feature of this condition.

A study of the pathological appearances is a little more rewarding, although in comparison with the wealth of symptoms and signs the findings at necropsy have been disappointingly few and difficult to interpret. There were no features of infective, granulomatous, or other form of cerebral inflammation. Perivascular cuffing was not observed, and inclusion bodies, although carefully

looked for, were not found. The neuronal loss was rather too widespread, and affected nerve-cells too different in site and function, for an 'abiotrophy' to be considered likely, most of such system disorders tending to affect neurones at fairly specific sites, or those which serve fairly well-defined functions. Moreover, the astroglial reaction, at least in the cases described by Alajouanine and van Bogaert (1950) extended beyond the areas of neuronal loss, leading the authors to believe that it could not have been solely reactive in type. In the first patient reported by Jones and Nevin (1954) the neuroglial reaction also 'extended into intact cortex'. The nature of the neuronal lesions, in our cases, did not explain the atrophy of nerve-cells. Loss of nucleoli, poor definition of the nuclear membrane, and vacuolation of the cytoplasm were observed in various combinations and at various sites, but these appearances have little diagnostic significance, being those of 'simple atrophy'. Cellular alterations of ischaemic or homogenizing type, as recorded in Case 2 of Alajouanine and van Bogaert (1950), were not encountered. Neurofibrillary tangles were not observed. A primary disease of the astroglia also seems improbable. Special attention was devoted to staining the glia, and in no instances did the glial cells appear degenerate, or their 'processes' diminished in number or of abnormal appearance. These points are mentioned because Foley and Denny-Brown (1955) have recently attributed to a primary degeneration of the protoplasmic astroglia an illness clinically resembling the one we have described. In their cases there was also variable status spongiosus and loss of nerve-cells, at times very gross; both these changes were considered to be secondary.

Jones and Nevin (1954) emphasized the presence of status spongiosus in their cases, and reviewed what is known about this condition. The brains of patients with general paralysis often show status spongiosus, which is particularly common in patients with marked focal symptoms. It is also seen in cases of air embolism (Lhermitte and Barrelet, 1934; Ameuille, Lhermitte, and Kudelski, 1935), and in close proximity to areas of haemorrhage into the white matter (Alajouanine, Thurel, and Hornet, 1936), and has been ascribed to tissue hydration, consequent upon altered vascular permeability. This in turn has been related to local circulatory disturbances. Most authors have held any associated neuronal changes to be ischaemic, and astrogliosis to be purely reactive. In support of their contention that the status spongiosus arose on a basis of vascular insufficiency in their cases, Jones and Nevin (1954) mentioned that in one of their patients unilateral cerebral oedema occurred, of a degree sufficient to cause a shift of the anterior cerebral artery, and that in their other patient obvious areas of softening, of classical ischaemic type, were observed in the basal ganglia. In the putamen one such area was in fact seen alongside a small area of status spongiosus, a finding considered to indicate 'a tissue reaction of different degree, most probably to the same kind of injury'. At first sight our findings might be thought to support the view of Jones and Nevin (1954) that the disease has a vascular basis; an intracerebral haemorrhage had occurred in our first patient, and both cortical and perivascular scarring were observed in our third case. The distribution of the lesions, moreover, with their apparent

predilection for the occipital cortex, might be argued to suggest tissue anoxia, for this area of the brain is particularly sensitive to such influences as altitudinal hypoxia or the anoxia of cardiac arrest. We do not, however, believe that vascular disease is the cause. If status spongiosus is the result of a critical disturbance of cerebral blood-flow, and if moreover such circulatory disturbance, however caused, is an important factor in this disease, one would expect most of the cases reported to have exhibited status spongiosus, to some degree at least. This is not the case. Status spongiosus is a variable finding in such patients. At times it may be conspicuous, as in Heidenhain's (1928) second case, in Hallervorden's (1930) case, in Case 1 of Jones and Nevin (1954), and in our third patient; on other occasions it has been slight, as in Case 2 of Jones and Nevin (1954) and in our first case; it may even be absent, as in the first patient described by Heidenhain (1928), in the cases described by Alajouanine and van Bogaert (1950), and in our second patient. Moreover, it cannot be argued that the presence or absence of status spongiosus is related to the duration of the illness. We have reviewed the published case reports with this possibility in mind, and no such correlation was found.

It should perhaps be emphasized that more than one clinical syndrome may arise on the pathological basis of status spongiosus, neuronal loss, and dense astrogliosis. A patient described by Meyer, Leigh, and Bagg (1954) died from a dementia of six months' duration, aged only 38, and rigidity, mutism, hypokinesia, and myoclonus had not been features of his illness. Necropsy revealed status spongiosus, neuronal loss, and dense astrogliosis. The cortical changes were diffuse, predominating in the occipital areas. No lesions were found in the basal ganglia, brain-stem, or cerebellum. It may well be that the additional involvement of these structures in our cases, although slight, has a profound effect on the clinical picture. This point of view finds some substantiation in the cases reported by Foley and Denny-Brown (1955), in which there was considerable involvement of the central grey matter and cerebellum, and in which 'bulbar myoclonus' was an outstanding feature.

One further suggestion has been made. Heidenhain (1928) considered his three cases to be closely related to the disease described by Creutzfeldt (1920) and Jakob (1923). Meyer, Leigh, and Bagg (1954) pointed out, however, that the histological changes found in Heidenhain's patients (which were also present in all the cases, subsequently published, cited at the beginning of the present paper) had not been present in Creutzfeldt's and Jakob's original cases, nor had they been observed in any of the patients reported to be suffering from the Creutzfeldt–Jakob syndrome up to 1954. The latter syndrome is clinically poorly defined, and seems to include a number of otherwise unclassifiable dementias presenting cross-relations to various systemic degenerations (McMenemey, 1941).

We regretfully conclude that the answer to the question 'What is the cause of this disease?' still eludes us completely. Clinical observation alone is unlikely to provide the solution, and from the observations here presented it will probably be inferred that the answer is unlikely to be found in the histological laboratory.

Intoxication, whether endogenous or exogenous, cannot yet be excluded, nor can acute selective degeneration of nerve-cells consequent upon the failure of some essential enzyme or accumulation of some toxic metabolite as yet unknown. It is along these lines that we feel further inquiry should be directed.

II. *Implications of the clinical findings.* It is difficult to reconcile this complex and distinctive syndrome with the paucity and banality of the lesions revealed at necropsy. This disparity illustrates most clearly the limitations of purely morphological interpretation. The occurrence in a given context of mutism, hypokinesia, decorticate posture, and myoclonus, must reflect a very unusual disturbance of neural function. We have therefore considered each symptom in turn in the light of current physiological beliefs, and suggest that this particular association implies a disorder at a high subcortical level. Our electroencephalographic findings are consistent with this view. The site of this functional disturbance may well explain the unusual features of the condition.

1. *Hypokinesia and mutism.* Various interpretations have been suggested to account for these phenomena. In the cases reported by Alajouanine and van Bogaert (1950) the striking poverty of voluntary movement and of speech were attributed to the intense rigidity affecting the whole musculature. In our first patient, however, mutism antedated the development of generalized rigidity by a week or two, and the development of trismus by at least a fortnight. The rigidity in the early stages was insufficient to have abolished all trace of voluntary movement. In our second case mutism also antedated the development of rigidity. Trismus never occurred; in fact the patient yawned frequently. In our third case dysphasia probably contributed to the difficulty in speech. Slight trismus was present at first, but could be readily overcome and, although mute, the patient could chew and swallow. She was immobile at a stage when the rigidity was not extreme. In the first of the patients described by Jones and Nevin (1954) rigidity was possibly a major factor in the development of akinesia and mutism, but in their second case the limbs were flaccid. It may finally be pointed out that in subacute inclusion encephalitis hypokinesia and mutism may be early symptoms, whereas marked rigidity is usually a late development. An alternative interpretation would relate hypokinesia and mutism to developing dementia. The analogy with subacute inclusion encephalitis is again instructive. In this condition Foley and Williams (1953) considered that the disintegration of speech 'runs parallel with the dementia, while its poverty is a reflection of the decline of volitional activity'. This explanation again cannot account for all the observed facts. We have recently seen a typical case of subacute inclusion encephalitis in which total mutism followed the herald symptom (a major convulsion). Mutism was obvious at a stage when comprehension was good, and when the child was ambulant, could play and feed itself, and had an almost normal range of activity. Involuntary movements, at first confined to the face, appeared a few days later, and obvious dementia only after a week or two.

We believe that certain observations made by the late Sir Hugh Cairns explain

the physiological basis of the hypokinesia and mutism shown by our patients. In 1941 Cairns, Oldfield, Pennybacker, and Whitteridge described a 14-year-old girl with an epidermoid cyst distending the third ventricle. She presented a most unusual appearance, for which they coined the term 'akinetic mutism'. 'In the fully developed state . . . [the patient] makes no sound and lies inert, except that the eyes regard the observer steadily or follow the movement of objects . . . despite the steady gaze, which seems to give promise of speech, the patient is quite mute . . . usually there are no movements of a voluntary character; no restless movements, struggling or evidence of negativism. Emotional movement is also in abeyance . . . the patient swallows readily but has to be fed. The condition is sometimes, though not always, associated with decorticate rigidity.' No improvement followed reduction of raised intracranial pressure by ventricular tapping. The cyst was then aspirated through the right lateral ventricle. Within 10 minutes the child gave her name, age, and address correctly, without any trace of dysarthria, co-operated perfectly in an examination, and got up within the next week. Five months later the patient relapsed into a state of akinesia and mutism, this time associated with a typical decorticate posture. There was again a dramatic response to tapping of the cyst, and all signs of extensor rigidity disappeared very soon. Further episodes occurred. The cystic part of the tumour was eventually dissected away, and she made an excellent recovery. The authors emphasized the fact that drowsiness was not a feature of her recurrent attacks of akinetic mutism, except during periods of severe decorticate rigidity. The open, moving eyes in fact gave her an appearance of alertness quite 'incongruous with her silence and general immobility'. From this excellently documented case report it will be seen that akinesia and mutism need not be directly related to drowsiness, dementia, or alterations of tone. The authors specifically stated that the mutism and loss of mobility were not dependent on decorticate rigidity. The disorder arose from pressure on the structures surrounding the third ventricle. Cairns (1952) later stated that he had seen akinetic mutism in other lesions near the third ventricle: with tumours of the pineal body or thalamus, in cases of thalamic haemorrhage, and after ventriculography or operation for the relief of severe hydrocephalus of the lateral and third ventricles from stricture of the aqueduct.

What the precise structure or structures are, disturbance of which produces this clinical state, remains uncertain. Cairns and his associates (1941) originally considered as a possible mechanism an interruption of impulses between the posterior hypothalamic and the medial thalamic nuclei. These fibres run immediately beneath the wall of the third ventricle and, after relay, project to the frontal areas. In his later writings, however, Cairns (1952) accepted the views of Magoun (1950) on the importance of the reticular formation of the brain-stem in the maintenance of the waking state. He considered that damage to this structure, or disturbance of the normal balance of entering afferent impulses, might result in various forms of impaired consciousness, of which akinetic mutism was one of the variants. We believe that the hypokinesia and mutism seen in our patients could well have arisen on the basis of a functional disorder at

this level. We doubt that they were merely the concomitants of rigidity or dementia.

2. *Rigidity and 'decorticate' posture.* All three of our patients ultimately developed a characteristic posture, the arms firmly adducted at the shoulders, the elbows flexed, the fists tightly clenched, and the lower limbs in rigid extension. So strongly clenched, in fact, were the fists in our third case that damage to the palms of the hands was sustained. Both patients reported by Alajouanine and van Bogaert (1950) presented a similar appearance, as did the first of the two patients described by Jones and Nevin (1954). The fact that the forearms were so firmly flexed in these cases implies a state of bilateral decortication rather than decerebrate rigidity. It will be recalled that in classical decerebrate rigidity, as described by Sherrington (1897–8) in the primate, the fore-limbs are held in rigid extension. Sherrington showed that the condition could not be due to a disturbance in the pyramidal tracts (since after unilateral ablation of the forebrain the rigidity developed ipsilaterally), and that it must therefore be due to interruption of some pathway already decussated at the level of section. In 1914 Magnus determined the limits between which such sections (in cat, dog, and rabbit) resulted in decerebrate rigidity: the section had to be above the level of the vestibular nuclei, and below that of the red nuclei. Decerebrate rigidity is probably due to release of the vestibular nuclei from extrapyramidal (rubrospinal) control. In primates, section of the brain-stem above the level of the red nuclei, or removal of the frontal lobes ('high' decerebration, or decortication) causes the upper limbs to assume a strongly flexed posture (Bieber and Fulton, 1938). 'Low' decerebrations in the primate (at or below the mid-collicular level of Sherrington) result in rigid extension of the upper limbs. This change in position of the upper limbs, according to the level of section, occurs on a background of rigid extension in the lower limbs. These facts have not always been taken into account in the earlier descriptions of 'decerebrate rigidity' in man. In clinical practice states of decortication are most often seen as a sequel of cerebral anoxia, or in patients with tumours or cysts in the region of the third ventricle. They are rare when the pathological process is cortical, sparing the subcortical white matter.

It will be recalled that in none of our cases were pyramidal signs much in evidence. The rigidity was largely extrapyramidal. 'Pseudo-bulbar' laughter and crying were not observed. The disturbance of tone in the patients of Alajouanine and van Bogaert (1950) was similar, being considerable, widespread, and liable to periodic exacerbations. The authors even referred to it as an *état de mal* (status epilepticus) of extrapyramidal origin. In the first patient reported by Jones and Nevin (1954), accesses of disturbance occurred, superimposed on the background of decorticate rigidity, in which the patient would flush, breathe deeply, and sweat profusely, and in which tachycardia, with elevation of the blood-pressure from its resting value of 140/90 to 200/120, would be observed. These accesses would be associated with a noticeable increase in frequency of the myoclonic jerks, and strongly suggest a paroxysmal discharge arising at a high diencephalic level. The typical decorticate posture in these patients must imply a functional disturbance in the regulation of tone

arising at a fairly high level. Disturbances arising below the level of the red nuclei would have been associated with decerebrate rather than decorticate rigidity. The paucity of pyramidal signs and the associated diencephalic fits suggest the uppermost part of the central grey matter as the possible site of this disorder. Purely cortical rigidities are rarely of this severity, and their clinical concomitants are rather different.

3. *'Myoclonic' involuntary movements.* All three of our patients exhibited sudden, brief, involuntary movements of varying frequency, amplitude, and distribution (although usually confined to the face and upper limbs), occurring singly, in small groups, or in runs lasting several minutes, both spontaneously and in response to various forms of sensory stimulation. The movements occurred either unilaterally or bilaterally, never affected agonists and antagonists simultaneously, were often sufficient to cause limb displacement, and lessened considerably but did not abate entirely during sleep. Their occurrence did not alter the already grossly abnormal electroencephalographic records, and at no time was generalization into a grand mal attack observed. (In one of the patients three grand mal attacks occurred, but were of sudden onset and not preceded by any noticeable increase in involuntary movements.) Whether some or all of these movements should be referred to as 'myoclonus' is largely a matter of definition, and useful definitions of myoclonus are notoriously lacking.

In the experimental animal myoclonus may occur in the absence of the cerebral cortex. Lorentz de Haas, Lombroso, and Merlis (1953) have recently shown that in cats the myoclonic response (to auditory and visual stimuli) produced by subconvulsant doses of metrazol is not abolished by complete decortication. Removal of the cortex merely raises the metrazol threshold. Neither the specific cortical sensory projection areas (visual, auditory) nor the motor cortex are therefore essential for the development of this type of myoclonus. Clinical evidence suggests, more specifically, that these movements originate in the subcortical grey matter. The benign myoclonus shown by many epileptics is now attributed to primary discharge in the upper part of the brain-stem or thalamus. The evidence for this view is considerable, and has been fully discussed by Penfield and Jasper (1954). Involuntary movements of myoclonic type are also seen in a number of progressive cerebral disorders in which the central grey matter is severely affected. In a recent detailed review of progressive familial myoclonic epilepsy (Unverricht's syndrome) Harriman and Millar (1955) pointed out that in this condition the involuntary movements are often precipitated by sensory stimuli, and that they are frequently of irregular occurrence and of asymmetrical distribution, although associated with bilaterally synchronous sharp waves in the electroencephalogram. Measurements of the time-intervals between cortical discharge and muscle contraction in this disorder suggest a primary subcortical discharge, probably in the brain-stem, responsible for both the myoclonus and the observed changes in the electroencephalogram. The pathological changes in such cases vary (Lafora bodies, lipoid inclusions, gliosis, or cell-loss) and are usually diffuse, but the brunt of the disorder not infrequently falls on the substantia nigra and dentate

nuclei. Watson and Denny-Brown (1955) found 'a prominence of intracellular accumulations of lipoid' in the thalamic and dentate nuclei in patients with cerebral lipoidosis. They had earlier (1953) shown that this condition was one of the causes of the syndrome of progressive myoclonic epilepsy. The same authors (1955) pointed out the similarity between 'stimulus-sensitive myoclonus' in cerebral lipoidosis and the early effects produced by strychnine. In both conditions an 'instability of the subcortical systems' is attributed to a breakdown of synaptic resistance. In certain organic cerebral diseases associated with myoclonus there is certainly sufficient structural alteration in the basal grey matter to account for such a phenomenon.

4. *Electroencephalography.* Two features are noteworthy in the tracings obtained from our patients. Both suggest a profound functional disturbance in the upper central grey matter, with widespread cortical repercussions. These features are: (1) the presence in Cases 1 and 3 of a dominant rhythm constituted by long runs (lasting up to 20 minutes) of regular, bilaterally synchronous, high-voltage polyphasic complexes at two per second. These were unaffected by the occurrence of involuntary movements and, under normal conditions, uninfluenced by various forms of sensory stimulation; and (2) the occurrence of characteristic 'suppression–burst' activity in the seconal-induced sleep record of Case 3, and the tendency to similar periodicity in the post-ictal sleep tracing in Case 2.

The paroxysmal occurrence of high-voltage, bilaterally synchronous, repetitive complexes of fairly constant form is realized most often by the petit mal attack. More elaborate synchronous complexes, occurring periodically, are a feature of certain diffuse neuronal disorders such as subacute inclusion encephalitis (Cobb and Hill, 1950; Clearkin and Millar, 1952; Hamoen, Herngreen, van Leeuwen, and Magnus, 1956), van Bogaert's sclerosing leucoencephalitis (Radermecker, 1949, 1951), and cerebral lipoidosis (Cobb, Martin, and Pampiglione, 1952; Watson and Denny-Brown, 1953), but in all these conditions the abnormal complexes are not continuous, but recur at either regular or irregular intervals, which may be of many seconds' duration. In none of these disorders have long sequences of uniform complexes, of the type here described, been found to constitute the dominant activity of the record during periods lasting several minutes. Of the 8,600 electroencephalograms performed in this Department since 1948, only those of the two patients under discussion were of this type. The electroencephalographic abnormalities reported by Jones and Nevin (1954) in their two cases did, however, resemble the present ones. Their first case showed 'an unusual pattern of polyphasic high-voltage complexes, synchronous in all areas, and occurring in long runs at a frequency of about one per second with a duration of $\frac{1}{4}$ to $\frac{1}{2}$ second'. In their second patient similar activity only developed terminally, and consisted of 'bilateral complexes, usually triphasic . . . present for periods lasting 10 to 15 seconds', occurring at a rate of about one per second. In patients of a similar age these particular electroencephalographic patterns seem to be characteristic of the condition here described.

The occurrence of 'suppression–burst' sequences in the sleep-activated

record of Case 3 is of considerable interest. This electroencephalographic pattern was first described in animals under deep barbiturate narcosis by Swank (1949) and Swank and Watson (1949). Lindsley, Bowden, and Magoun (1949) recorded similar cortical activity after lesions of the basal diencephalon in cats. Mesencephalic transection or lesions of the basal diencephalon were considered as freeing the cortex from the influence of activating mechanisms in the brain-stem. The more rostral the cut in the reticular core of the brain-stem, the greater became the degree of electrocortical synchrony. In 1952 Henry and Scoville described their electrographic recordings from the isolated human cortex. In 33 of 34 patients submitted to unilateral or bilateral prefrontal lobotomy, under local as well as under thiopentone anaesthesia, characteristic suppression–burst activity was recorded from the undercut cortex. The activity was confined to isolated cortex, and was not seen from leads lateral and posterior to such an area. It took the form of bursts of fast activity (often followed by one or two high-voltage, very slow delta waves) alternating with periods of almost complete electrical quiescence. This pattern persisted for at least a year, and could not have been due to the immediate effects of injury. The authors considered this spontaneous rhythmic behaviour to be a 'fundamental' property of organized neurones, and 'possibly related to the release of cortex from the influence of the reticular activating system'.

In clinical practice 'suppression–burst' activity in the electroencephalogram is distinctly rare. It is not a feature of normal or of seconal-induced sleep, nor is it encountered in cases of cerebral neoplasm, after trauma, or in the common toxic, infective, or degenerative cerebral disorders. Radermecker (1949) first observed a rhythm of this type in patients with van Bogaert's sclerosing leucoencephalitis, Martin, Macken, and Hess (1950) in an illness with features of both sclerosing leucoencephalitis and subacute inclusion encephalitis, and Cobb and Hill (1950) in the late stages of subacute inclusion encephalitis.[2] In one of Cobb and Hill's cases the terminal record 'showed an absence of rhythm, broken periodically by . . . a complex having remarkable constancy of wave form'. The authors emphasized the fact that expert pathological investigation had not suggested a single structure, deep in the brain, which was invariably affected in this disease; yet, as they pointed out, the lesions of subacute inclusion encephalitis are so diffuse that this possibility can by no means be excluded. Their findings have been amply confirmed by subsequent observers (Hamoen, Herngreen, van Leeuwen, and Magnus, 1956). The electroencephalogram of a case of cerebral lipoidosis, reported by Watson and Denny-Brown (1953) also showed 'periods of relative electrical inactivity'. Reports of sleep-induced 'suppression–burst' activity are even more scarce. Silverman (1956) has recently reviewed the use of sleep as a general activation procedure in electroencephalography, but did not mention this phenomenon. We have found only two published reports of its occurrence. Kirstein (1954) described an eight-

[2] Current opinion increasingly holds that the sclerosing leucoencephalitis of van Bogaert and subacute inclusion encephalitis have many features in common, and may well be the same disease (Greenfield, 1950; Malamud, Haymaker, and Pinkerton, 1950; Martin, Macken, and Hess, 1950; Foley and Williams, 1953).

month-old girl suspected of having suffered from mild encephalitis of unknown aetiology, the presenting symptom of which was recurrent myoclonic spasms. The waking electroencephalogram was diffusely abnormal. During sleep 'suppression–burst' sequences were observed. The author considered that this characteristic pattern might be expected during sleep in a patient with a lesion affecting the reticular system, as 'one would then obtain . . . a more complete "isolation" of the cortex than during sleep in a normal person'. The other report is by Vizioli (1955). A woman of 62 had had several attacks of status epilepticus in the previous two years. There were no neurological signs, and the encephalogram was normal. The waking electroencephalogram was of the 'low-voltage, fast' type, but pentothal-induced sleep, lasting 20 minutes, produced bilaterally synchronous bursts of high amplitude at 12 to 14 cycles per second, separated by 'blackouts of electrical activity lasting from four to seven seconds'. Although the diagnosis was obscure, the author suggested that artificial sleep had, in this case also, 'blocked' the reticular system, producing a more complete 'isolation' of the cortex than ever occurs during sleep in normal subjects.

Both types of electroencephalographic abnormality recorded in our patients suggest a disturbance arising in the uppermost part of the brain-stem. The direct and indirect projections to the cortex from certain ganglionic masses in the thalamic region are extensive, and it has been shown that abnormal electrogenesis in even small areas of the deep grey matter rapidly results in synchronous activation of large areas of both hemispheres. Such a mechanism might account for the unusual dominant rhythms seen from time to time in Cases 1 and 3. It is improbable that these symmetrical, bilaterally synchronous, and widespread wave-and-spike types of dysrhythmia could have arisen at an exclusively cortical level, especially when the scantiness of morbid changes in certain parts of the brain is recalled (in the frontal areas, for instance, where abnormal rhythms were particularly well sustained). Morphological changes were rather more definite in the thalamic regions. At this level, moreover, the paucity of structural change ceases to be an argument against the local origin of the discharge. Paroxysmal disturbances at this site, often with widespread cortical repercussions, usually have no demonstrable pathological substratum. The presence of 'suppression–burst' activity in the record in Case 3 during seconal-induced sleep also points to considerable instability of central electrogenesis. A small dose of barbiturate induced changes in cortical activity suggestive of almost total de-afferentation. It is unlikely that these changes would have occurred without antecedent impairment of those mechanisms in the basal grey matter concerned in the regulation of cortical rhythms.

Conclusions

The pathological findings in these cases were few and difficult to interpret. The clinical features were so striking and distinctive, however, that it was hoped that neurophysiological analysis might answer some of the questions left unanswered by the microscope.

Taken alone, neither hypokinetic mutism nor decorticate posture necessarily indicate a disturbance of subcortical (upper brain-stem) mechanisms, although, for reasons previously stated, their association is rather suggestive of a disorder at this site. The occurrence of myoclonus and of the particular electroencephalographic patterns observed in these patients also suggests such a 'subcortical' disorder. When all the data, both clinical and electroencephalographic, are taken into account, it is difficult to see how else the findings can be interpreted. It is our tentative conclusion that it is precisely because the brunt of the functional disorder falls on subcortical structures that the disease we have here described differs so markedly in its manifestations from all other 'degenerative' disorders of the nervous system.

Acknowledgements

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Summary

Three cases are described of an illness, of subacute onset and steady progression, occurring in middle-aged persons, and ending fatally in from 10 to 18 weeks. The condition is characterized by personality change, mutism, hypokinesia, decorticate rigidity, and involuntary movements of myoclonic type. The electroencephalographic findings were very abnormal, and may prove to be helpful in diagnosis.

At necropsy the brains showed no evidence of encephalitis, neoplasm, or significant cerebro-vascular disease. The pathological findings were scanty when compared with the striking clinical features. The most constant findings were neuronal loss, affecting mainly the cortex and central grey matter, together with astrogliosis, at times intense, and a tendency to status spongiosus.

The mutism, hypokinesia, decorticate posture, and involuntary movements exhibited by these patients are analysed in turn in the light of current neurophysiological beliefs, and it is concluded that their association indicated a profound functional disturbance arising in the central grey matter. The electroencephalographic findings support this view.

Similar cases from the literature are reviewed. No firm conclusion as to aetiology can be reached on the basis of the data so far recorded.

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FIG. 4. Case 1. Eighth week of illness. Characteristic 'decorticate' posture of upper limbs

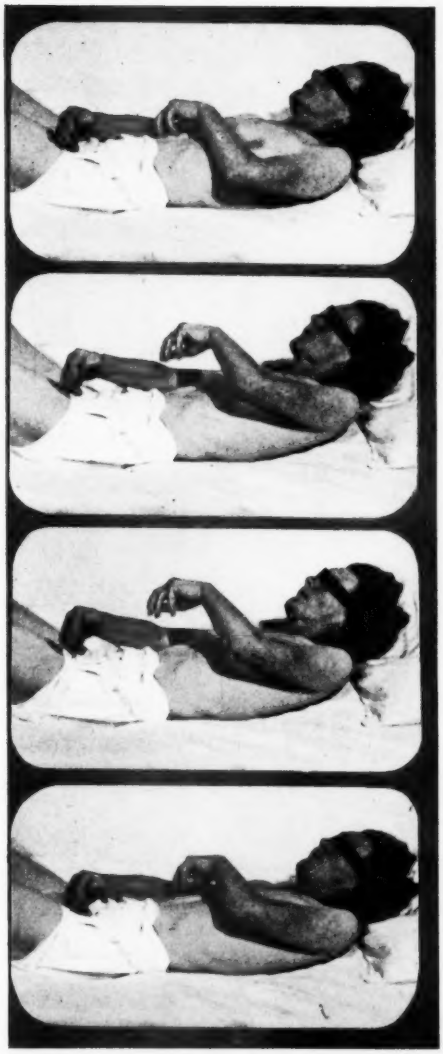

FIG. 5. Case 3. Twelfth week of illness. Response to auditory stimulus (hand-clap). Every fourth frame of a cine-film has been reproduced. The total duration of this spasm was 1·2 second

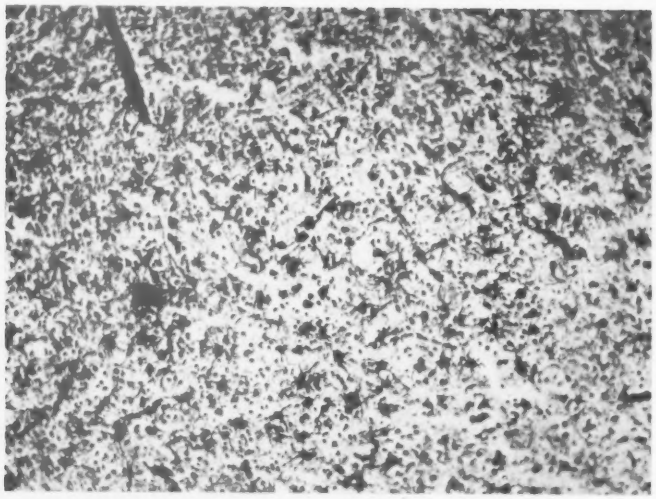

FIG. 6. Case 1. Calcarine cortex. Glial proliferation. (Hortega method for astrocytes, ×90)

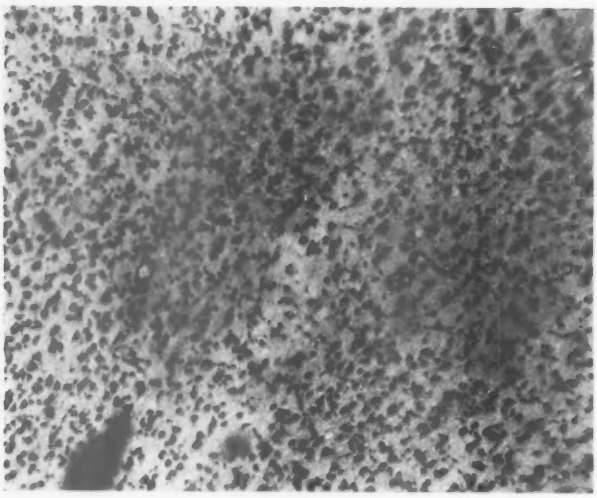

FIG. 7. Case 1. Occipital cortex. Loss of nerve-cells and astroglial proliferation (Nissl's stain, ×90)

FIG. 8. Case 3. Occipital cortex. Glial scarring can be seen on the surface of some of the gyri and throughout the cortex. The status spongiosus is apparent in some convolutions, even at this low power (Phosphotungstic-acid-haematoxylin, ×2)

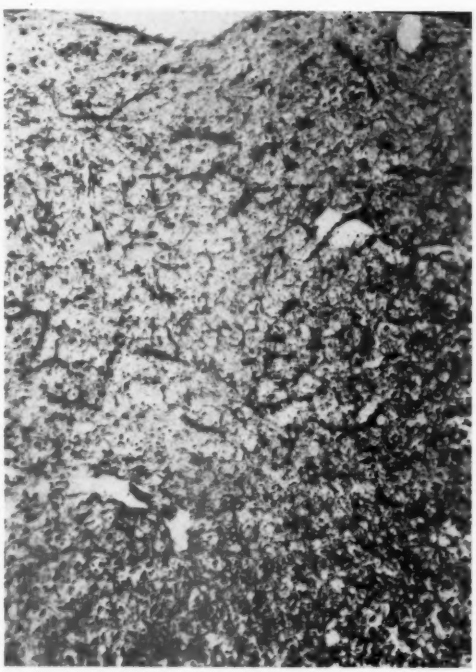

FIG. 9. Case 3. Occipital cortex. Paucity of nerve-cells. Slight gliosis. Status spongiosus (Bielschowsky's stain, ×90)

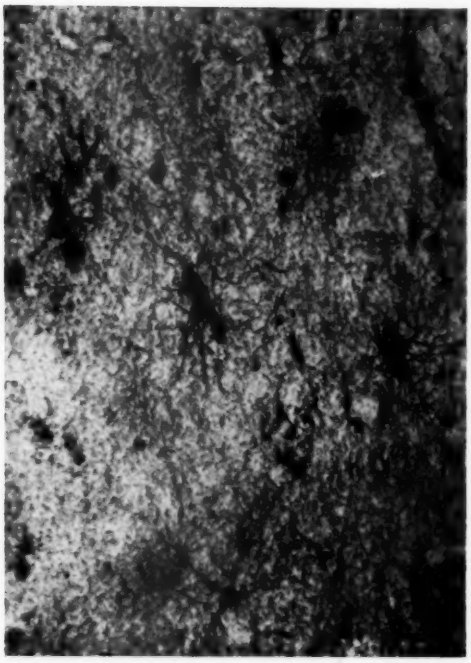

FIG. 10. Case 3. Glial proliferation in the mid-brain (Holzer's stain, ×360)

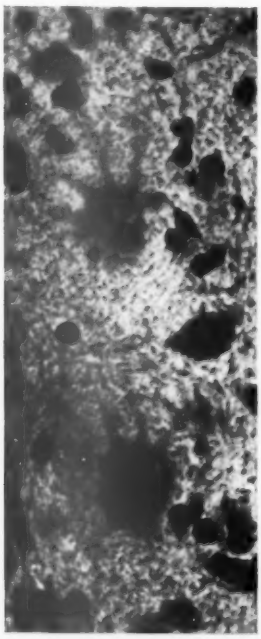

FIG. 11. Case 3. Dentate nucleus. Some of the cells are grossly swollen and very pale, and have spiky processes (Nissl's stain, ×360)

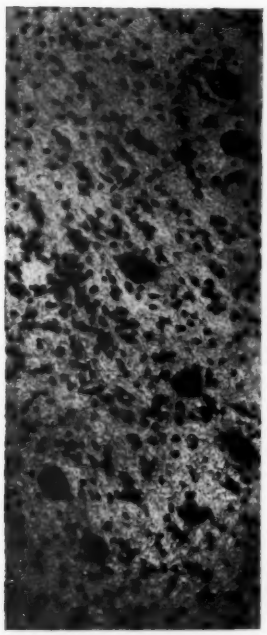

FIG. 12. Case 3. Dentate nucleus. Slight excess of glial elements, with occasional neuronophagia (Nissl's stain, ×90)

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OBSERVATIONS IN MAN UPON THE OSMOTIC BEHAVIOUR OF THE BODY CELLS AFTER TRAUMA[1]

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It has long been recognized that for some days after surgical operations the serum-sodium and serum-chloride levels tend to be low, even without loss to the body of sodium and chloride (Coller, Bartlett, Bingham, Maddock, and Pedersen, 1938; Ariel, Abels, Pack, and Rhoads, 1943; Moore and Ball, 1952; Wynn and Rob, 1954; Zimmermann, Casey, and Bloch, 1956). So common is this biochemical finding that it has become accepted as part of the normal metabolic response to trauma (Moore and Ball, 1952; Zimmermann, Casey, and Bloch, 1956; Wilson, Edelman, Brooks, Myrden, Harken, and Moore, 1954). The serum-sodium and serum-chloride levels are usually lowest on the first and second days after operation; the effect persists for several days, and sometimes even longer. Serum hypotonicity, or hyponatraemia as it is sometimes called, is usually greatest and most prolonged with extensive operations, and especially after operations on the heart (Wilson, Edelman, Brooks, Myrden, Harken, and Moore, 1954; Goodyer and Glenn, 1955). Coincidentally with these serum changes, total body sodium and (to a lesser extent) chloride are usually increasing (unless there is extrarenal loss of sodium) because of the low renal excretion of these ions. The apparent metabolic anomaly of a falling serum-sodium concentration with total excess of sodium in the body has been termed by Moore and Ball (1952) the 'sodium paradox'. Usually the serum hypotonicity which follows trauma is of moderate extent and symptomless, but severe hypotonicity is not infrequent, and may produce serious symptoms (Wynn and Rob, 1954).

The cause of serum hypotonicity after trauma, when sodium is being retained, has recently been extensively investigated, but with conflicting results. The following seem to be the main possible causes, acting either singly or in combination. First, water may be retained in osmotic excess of electrolytes, thus diluting the body-fluids (Deming and Gerbode, 1953; Wynn and Rob, 1954). According to Zimmermann, Casey, and Bloch (1956) water retention alone is inadequate to account for the apparent disappearance of sodium. Other authors, for example, Dudley, Boling, Le Quesne, and Moore (1954), Wilson, Edelman, Brooks, Myrden, Harken, and Moore (1954), and Wilson (1955), have reached the same conclusion. They have suggested that serum hypotonicity after operation is caused, partly at least, by the movement of sodium into a site where it becomes 'osmotically inactive', in cells, in connective tissue, in bone, or

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within the gut. Allied to this theory is the possibility that, in some unexplained way, the osmotic activity of the cell-solutes is lowered without water passing into or solutes passing out of the cells. Such a mechanism has been inferred by Elkinton, Winkler, and Danowski (1944–5) to account for changes in extracellular osmolarity in a variety of water and electrolyte disturbances, and they termed the process involved the 'osmotic inactivation of cell base'. A third theory, advanced by De Cosse, Randall, Habif, and Roberts (1956) is that serum hypotonicity following trauma is due to the movement of cell-water in excess of cell-solutes to the extracellular fluid, the osmolarity of this fluid therefore falling while that of the cells rises. Unequal osmolarity inside and outside cells was also implied by Graber, Beaconsfield, and Daniel (1956), who claimed that cortisone, administered in severe hypotonicity after operation, caused the movement of hypotonic fluid into the cells. Unlike the first explanation of serum hypotonicity after operation, the other theories mentioned involve unorthodox views on the osmotic behaviour of cells for which there is very little evidence. The purpose of the present investigation was to establish whether the effect of trauma (surgical and otherwise) on serum-electrolyte levels could be accounted for according to orthodox views, by change in the external water and electrolyte balance, or not.

Theory

According to the classical views of Gamble, Ross, and Tisdall (1923) there is osmotic equality between the cells and the extracellular fluid, and a change in the osmolarity on either side of the cell-membrane is followed by a redistribution of water, or solutes, or both, until equilibrium is re-established. Except in hyperglycaemia, the effective osmolarity of the body-fluids, upon which the distribution of water across the cell-membrane depends, is measured, as a close approximation, by the total electrolyte concentration of the body-fluids (Leaf, Chatillon, Wrong, and Tuttle, 1954) (for simplicity, complete dissociation of the electrolytes is assumed). The external balance of the osmotically active electrolytes (mainly the salts of sodium and potassium) measures the change in the total amount of such solutes in the body. The cation and anion concentrations of the extracellular fluid are nearly equal, and, in the common water and electrolyte disturbances seen clinically, changes in the electrolyte balance usually involve approximately equal amounts of cations and anions. Osmotic stresses, as far as water and electrolytes are concerned, can therefore be depicted with reasonable accuracy by using the total cation concentration of the extracellular fluid to measure the effective[2] osmolarity of this fluid, and the external cation (sodium plus potassium) balance to measure changes in the osmotically active solute content of the body. The relation between change of

[2] Effective osmolarity refers to the concentration of those solutes to which the cell-membrane is impermeable, or which are held by electrostatic forces. Thus, for example, urea, which diffuses freely across cell-membranes, does not affect the distribution of water across the membrane, and hence does not contribute to the effective osmolarity of the body-fluids.

total cation concentration in the extracellular fluid and change of total body-water and external electrolyte balance is given by the following formula (Elkinton, Winkler, and Danowski, 1944–5; Wynn, 1956):

$$W_1[B_1]+bB = W_2[B_2],$$

where

W_1, W_2 = initial and final total body-water (litres),
$[B_1]$, $[B_2]$ = initial and final total cation concentration in the extracellular fluid (mM. per litre), and
bB = the external cation balance (sodium plus potassium (mM.)).

For the derivation of these quantities see *Chemical methods*.

The formula accurately predicts the change in total cation concentration in the serum (and, presumably, extracellular fluid) in dogs given an excess of water (Leaf, Chatillon, Wrong, and Tuttle, 1954; Wynn, 1955) and an excess of sodium salts[3] (Wolf and McDowell, 1954). As mentioned above, the evidence is conflicting as to whether the formula applies to osmotic stresses in man after trauma and in disease. It is especially to be noted that in this formula potassium is given the same osmotic value as sodium. Whether or not changes in the potassium balance produce changes in extracellular osmolarity which accord with the osmotic theory formulated here, is a subject upon which evidence is incomplete, and it will be examined further in the present studies.

In applying the formula it is important that serum-glucose levels remain relatively constant, since the osmotic effect of glucose, when it is being metabolized, is not predictable with the same certainty as it is when not metabolized (Wynn, 1954, and unpublished observations). In the balance studies described here, changes of serum-glucose less than $\pm$50 mg. per 100 ml. (2·7 mM. per litre) were disregarded. Above this level the balance study concerned was excluded from consideration. This occurred on three out of 53 occasions. It is also important that acid-base balance should not be greatly disturbed, since the movement of H^+ between cells and the extracellular fluid would affect certain of the approximations used in deriving the osmotic formula (Swan and Pitts, 1955), and the same would apply if the urine were alkaline in reaction. None of the patients studied here had primary acid-base disorders, nor did detectable alkalosis develop in those patients who became depleted of potassium, as will be mentioned later. Finally, changes in the balance of calcium and magnesium, and in the serum value of these ions, are disregarded, as being small and having negligible influence on the osmolarity of the body-fluids (Wynn, 1955).

The use of the formula of prediction. By measuring total body-water, serum-electrolytes, serum total protein, water-content, pH, and glucose concentration, and the external balance of water, electrolytes, and nitrogen, it is possible to predict the changes in serum osmolarity (that is, in sodium plus potassium) from day to day, and to compare the values with the observed values. If the

[3] Further studies by these authors (McDowell, Wolf, and Steer, 1955) may lead to some modification of the osmotic theory described here, without affecting the conclusions as far as changes in total cation concentration in the serum, after the infusion of sodium salts, are concerned.

observed and predicted values for total cation concentration in the serum (and hence in the extracellular fluid) differed more than could be accounted for by experimental error and the approximations involved in the prediction formula, then it would be apparent that the osmotic theory upon which it is based did not apply to the situation following trauma. If the osmotic formula is an accurate method of prediction, it should apply equally whether the water and electrolyte balance causes a decrease or an increase in serum osmolarity.

Metabolic studies were carried out on patients after trauma, and the formula was applied in two ways. First, each 24-hour period was regarded as a separate experiment, and the appropriate values were used to calculate $[B_2]$, which was compared with the observed value for $[B_2]$. The observed $[B_2]$ became the observed $[B_1]$ for the subsequent 24-hour balance period, and so on until the end of the study. The second method was to calculate $[B_2]$ from the progressive balance figures from the beginning to the end of the study. Thus only two plasma values were used in the latter calculation—the initial value before trauma and the final value.

Subjects

Three groups of patients were studied. *Group A* consists of seven patients who underwent major surgery with general anaesthesia (Cases 1 to 7). The type of operation is recorded in Table I. Metabolic balances were carried out for five days after operation in four patients, and for three days in three patients. All patients received only intravenous fluids and occasional small drinks. Throughout the balance period the intake of water and electrolytes was adjusted to avoid gross distortion of the balance, but there were several 24-hour periods in which fairly large changes could not be avoided.

Group B. The three patients in this group underwent operations. In Case 8 a laparotomy had been done 24 hours before for a carcinoid tumour involving the liver, and the patient had suffered a period of cardiac arrest necessitating cardiac massage. A large amount of hypertonic saline was infused over a period of three hours, and metabolic measurements were carried out subsequently for 24 hours. At the time of the infusion the patient was unconscious, and the infusion was given to treat presumed cerebral oedema. This case is included as an example of hypernatraemia following operation, in order to test the accuracy of prediction when the serum-sodium level rises greatly. The remaining two patients (Cases 9 and 10) developed after operation a marked serum hypotonicity, mainly due to water retention, but had no symptoms. The lowest sodium levels in these patients were comparable to those observed by Wilson, Edelman, Brooks, Myrden, Harken, and Moore (1954) after mitral valvotomy. Case 9 was studied for five days after operation, and Case 10 for two days.

Group C. There are three medical patients in this group (Cases 11, 12, and 13), all of whom were previously well, and were admitted to the metabolic ward within an hour of the onset of their illnesses. One patient (Case 11) had a severe myocardial infarction, with pain and prolonged fall of blood-pressure,

the latter lasting two days and requiring continuous noradrenaline infusion for its treatment. The second (Case 12) had a less severe myocardial infarction. The third patient (Case 13) had a dissecting aortic aneurysm (confirmed at autopsy), producing severe pain which recurred several times during the balance study. These patients were studied for five days; in Cases 11 and 13 only intravenous fluids were given; the other patient (Case 12) took a light, mainly liquid, diet by mouth. Our purpose in this group was to study the effect upon serum-electrolytes of trauma other than that of operation, and to compare the findings with those obtained in the subjects in Group A.

Metabolic Methods

The patients were studied in a metabolic ward during the winter months. The methods of weighing the patients were as follows. Patients confined to bed were weighed on special scales (Avery type 33N), which weighed the whole bed. The scales are sensitive to 30 gm., and were checked by certified weights. The bed and the movable items were weighed separately, in case the latter required replacement. The patients were weighed naked, covered by a sheet only. As soon as possible, when the patient became ambulant, and always at the end of the study, the weight of the bed and other items was checked. On only two occasions was there a significant change (+200 gm. in each case) due to uptake of moisture by the sheets. It was assumed that this had been progressive, and body-weight changes were corrected accordingly. Ambulant patients were also weighed on personal weighing scales sensitive to 15 gm. (Avery type 3302 ABN), and the weights shown by the two methods agreed closely. Body-weights were measured immediately before operation, or when the patients (in Group C) were admitted to the ward, and subsequently daily. Blood lost at operation was measured, and replaced quantitatively by stored blood. The sodium and water content of the sodium citrate solution used as an anticoagulant was taken into account in assessing the water and sodium balance. Operation specimens were weighed in the fresh state, and body-weight corrected accordingly. The weight and volume of all intake, excreta, and aspirations were measured. At the end of the balance period total body-water was estimated. The daily balance period commenced at 10 a.m., so that the first period after operation was often less than 24 hours. At about 8 a.m. the intravenous infusion was slowed down, to ensure that blood taken two hours later represented as far as possible the state of equilibrium.

Calculation of water and electrolyte balance. The water balance was calculated from an adaptation of the formula of Lavietes (1935):

$$W = (Wt_2 - Wt_1) + (Se - Si) + Ci + Fb + 3{\cdot}38Nu,$$

where

W = water balance (ml.),
Wt_1, Wt_2 = initial and final body-weight (gm.),
Se, Si = solids of the excreta and ingesta (gm.),
Ci = carbohydrate ingested (gm.)

Fb = fat burned (gm.),
Nu = urine nitrogen (gm.),

$$\text{Fat burned } (Fb) = \frac{\text{I.L.} - 2{\cdot}12Ci - 10{\cdot}6Nu}{3{\cdot}78}$$

(I.L. = insensible loss of weight = $(Wt_1 - Wt_2) + (wf - we)$ when wf and we are the weight of intake and excreta.)

The solids of the intake were measured by drying weighed aliquots to constant weight at 105° C. The urine solids were calculated by Long's coefficient (1903): urine solids (gm.) = 2·66 × the last two figures of the urinometer reading × the urine volume in litres. The electrolyte and nitrogen balance was measured in the usual way as the difference between intake and output. Daily loss of electrolytes in sweat was assumed to be 5 mM. of NaCl for a person weighing 60 kg. or less, and 7 mM. for subjects weighing about 70 kg. On very few occasions was there visible sweating, and no additional allowance was made for this.

Chemical methods. Serum and urine electrolytes, serum total protein and non-protein-nitrogen, urine total nitrogen, serum-glucose, haemoglobin, haematocrit value, and blood and urine pH were estimated in duplicate according to methods previously described (Wynn and Rob, 1954). Serum-water was determined by drying serum to constant weight at 105° C. Total cation concentration in the extracellular fluid [B] was calculated from the serum-sodium and serum-potassium values, the former being corrected for serum water-content and the Donnan effect, as described elsewhere (Wynn, 1955). Serum-calcium and serum-magnesium levels were assumed to be constant at 3·5 mM. per litre (Wynn, 1955). Total body-water was estimated at the end of the period of study by the antipyrine method (Soberman, Brodie, Levy, Axelrod, Hollander, and Steele, 1949), and the initial total body-water calculated from the water balance for each day (see *Calculation*). Blood lost at operation was estimated from the haemoglobin-content of the swabs, packs, and towels used at the operation.

Analytical and other errors. The standard deviation of 10 sodium determinations on the same serum sample was 0·7 mM. per litre. The standard error for the mean of duplicate determinations is therefore 0·5 mM. per litre. The effect of errors in the calculated water and electrolyte balance can be assessed from the following data. If the total body-water is 36 litres, an error of 18 mM. in the external balance of sodium plus potassium causes an error of 0·5 mM. per litre in the predicted value of [B_2]. If the error in the calculated water balance is 200 ml., the error in the predicted value of [B_2] is approximately 0·8 mM. per litre. If the measurement of total body-water is in error by 5 per cent., and the change of water balance is one litre, the error in calculating [B_2] is approximately 0·2 mM. per litre. If the change of water balance is three litres, the error in [B_2] in the above example is about 0·5 mM. per litre. We believe that the analytical and balance techniques used were not subject to errors greater than these examples, and that the errors were not systematic, but there is no way of proving this. Another potential source of error in applying the prediction

formula lies in the small 'spontaneous' variations which can be observed in the serum-sodium level in a given subject over short periods of time, which do not seem to be explained by changes in the external water and electrolyte balance (Fawcett and Wynn, 1956). The largest change of this kind that we have observed in a healthy person is 1·5 mM. per litre occurring in 15 minutes. Over a large number of estimations, however, it is unlikely that such changes would bias the results systematically.

TABLE I

Case number	*Sex*	*Body-weight (kg.)*	*Total body-water* (litres)*	*Trauma*
1	F	59·30	29·60	Hiatus hernia repair
2	M	54·87	38·40	Nephrectomy for hypernephroma
3	M	58·75	32·30	Partial gastrectomy for duodenal ulcer
4	M	68·00	36·70	Partial gastrectomy for duodenal ulcer
5	M	79·60	47·00	Acute small-bowel obstruction. Division of adhesions
6	F	42·46	23·40	Biliary cirrhosis. Drainage of hepatic ducts
7	F	70·33	28·13	Hysterectomy for fibromyomata
8	M	66·55	35·60	Carcinoid tumour with hepatic metastasis. Laparotomy
9	F	100·15	37·55	Cushing's syndrome. Adrenalectomy
10	F	62·30	33·65	Appendicectomy
11	M	73·83	40·60	Severe coronary occlusion
12	M	56·42	33·85	Moderate coronary occlusion
13	M	70·62	35·30	Dissecting aortic aneurysm

* The total body-water is the initial value, as calculated from the antipyrine space, corrected for change of water balance from zero time to the time of the antipyrine measurement (see *Metabolic Methods*).

Results

Table II records the intake, output, and changes in external balance of water, sodium, potassium, and chloride for 52 twenty-four-hour balance periods in all the patients. The progressive balance from the beginning to the end of the study in each patient is also recorded. On 26 days the intake of water and electrolytes, and the external balances, were not larger than might be expected to occur in healthy subjects, so that on these days, unless trauma (from operation or otherwise) were itself to have an effect, large changes in $[B]$ (assumed to be more than 4 mM. per litre) over one 24-hour period were not to be expected. In 16 of the remaining 26 balance periods (marked by an asterisk in Table II) the intake and output of water and electrolytes were larger than would normally be encountered in subjects not receiving parenteral fluids; but the change in external water and electrolyte balance was not large (predicted change of $[B]$ in 24 hours less than 4 mM. per litre). In 10 twenty-four-hour periods, marked by a † in Table II, the change in water and electrolyte balance was sufficient to cause a predicted change of $[B]$ greater than 4 mM. per litre. In these cases the average of the predicted changes (disregarding sign) was 11·9 mM. per litre (Table IV). Thus it is possible to compare the accuracy of the formula of prediction when the intake, output, and balance of water and electrolytes were small, when the intake and output were large, but the balance was small,

TABLE II

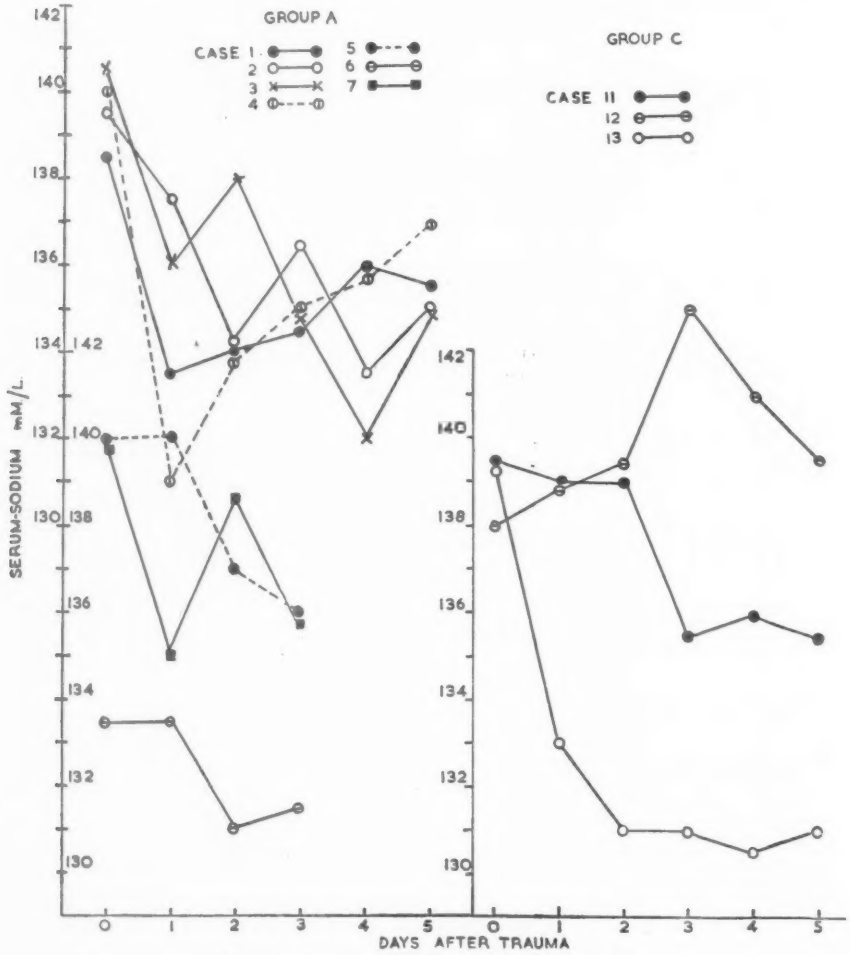
Twenty-four-hour and Progressive External Balance Data in 10 Surgical and Three Medical Cases

	In(x)				*Out(y)*				*Balance*				*Progressive Balance*			
Case number	H_2O (*ml.*)	*Na* (*mM.*)	*K* (*mM.*)	*Cl* (*mM.*)	H_2O (*ml.*)	*Na* (*mM.*)	*K* (*mM.*)	*Cl* (*mM.*)	H_2O (*ml.*)	*Na* (*mM.*)	*K* (*mM.*)	*Cl* (*mM.*)	H_2O (*ml.*)	*Na* (*mM.*)	*K* (*mM.*)	*Cl* (*mM.*)
1†	2,102	92	0	77	1,480	78	53	73	+622	+14	−53	+4	+622	+14	−53	+4
	2,351	139	42	181	2,160	65	49	89	+191	+74	−7	+92	+813	+88	−60	+96
	1,630	3	57	31	2,620	122	44	144	−990	−119	+13	−113	−177	−31	−47	−17
	1,725	18	9	20	2,040	73	36	96	−315	−55	−27	−76	−492	−86	−74	−93
	1,633	60	58	54	1,550	48	37	46	+83	+12	+21	+8	−409	−74	−53	−85
2	2,137	106	0	79	1,736	41	30	46	+400	+65	−30	+33	+400	+65	−30	+33
†	4,835	14	24	19	4,690	121	76	148	+145	−107	−52	−129	+545	−42	−82	−96
*	4,503	550	56	555	2,090	138	30	157	+2,413	+412	+26	+398	+2,958	+370	−56	+302
*	1,184	24	28	30	2,475	271	50	259	−1,291	−247	−22	−229	+1,667	+123	−78	+73
*	1,550	61	49	45	2,800	181	45	169	−1,250	−120	+4	−124	+417	+3	−74	−51
3‡	1,400	79	0	67	1,055	46	79	44	+345	+33	−79	+23	+345	+33	−79	+23
	2,225	77	27	104	1,580	15	40	18	+645	+62	−13	+86	+990	+95	−92	+109
*	4,571	75	0	75	3,900	20	27	29	+671	+55	−27	+46	+1,661	+150	−119	+155
*	3,490	0	0	0	3,090	34	29	51	+400	−34	−29	−51	+2,061	+116	−148	+104
†	1,479	12	22	13	3,125	15	17	29	−1,646	−3	+5	−16	+415	+113	−143	+88
4‡	1,875	85	0	85	2,250	142	89	162	−375	−57	−89	−77	−375	−57	−89	−77
*	3,093	225	5	175	1,853	42	45	64	+1,240	+183	−40	+111	+865	+126	−129	+34
	2,143	175	2	150	2,120	79	49	115	+23	+96	−47	+35	+888	+279	−176	+69
	1,722	165	0	165	2,050	133	43	123	−328	+32	−43	+42	+560	+311	−219	+111
	1,305	23	45	35	1,400	101	29	90	−95	−78	+16	−55	+465	+233	−203	+56
5‡	1,653	76	0	76	1,350	88	64	104	+303	−12	−64	−28	+303	−12	−64	−28
	2,182	65	0	65	2,150	65	58	79	+32	0	−58	−14	+335	−12	−122	−42
	2,129	32	0	32	2,320	79	61	133	−191	−47	−61	−101	+144	−59	−183	−143
6	900	0	0	0	1,145	32	54	40	−245	−32	−54	−40	−245	−32	−54	−40
	2,290	37	41	40	1,935	37	40	36	+355	0	−1	+4	+110	−32	−55	−36
	2,300	45	50	34	2,300	37	48	34	0	+8	+2	0	+110	−24	−53	−36

Case number	*In(x)*				*Out(y)*				*Balance*				*Progressive Balance*			
	H_2O (*ml.*)	*Na* (*mM.*)	*K* (*mM.*)	*Cl* (*mM.*)	H_2O (*ml.*)	*Na* (*mM.*)	*K* (*mM.*)	*Cl* (*mM.*)	H_2O (*ml.*)	*Na* (*mM.*)	*K* (*mM.*)	*Cl* (*mM.*)	H_2O (*ml.*)	*Na* (*mM.*)	*K* (*mM.*)	*Cl* (*mM.*)
7	1,300	80	0	65	930	28	97	88	+370	+52	−97	+7	+370	+52	−97	+7
*	2,827	188	44	195	2,030	37	27	55	+797	+151	+17	+140	+1,167	+203	−80	+147
	2,285	42	23	41	2,560	152	17	142	−275	−110	+6	−101	+892	+93	−74	+46
8†	1,762	562	0	562	2,198	111	71	148	−436	+451	−71	+414	−436	+451	−71	+414
9‡†	6,200	0	0	0	1,615	84	76	107	+4,585	−84	−76	−107	+4,585	−84	−76	−107
†	3,380	433	0	433	4,204	75	55	65	−824	+358	−55	+368	+3,761	+274	−131	+261
†	4,075	308	0	308	7,045	308	54	293	−2,970	0	−54	+15	+791	+274	−185	+276
*	3,665	232	0	232	3,865	165	55	210	−200	+67	−55	+22	+591	+341	−240	+296
*	4,975	311	8	312	4,236	212	24	244	+739	+99	−16	+68	+1,330	+440	−256	+364
10‡†	6,560	0	0	0	2,460	119	118	125	+4,100	−119	−118	−125	+4,100	−119	−118	−125
†	210	0	0	0	5,910	79	24	58	−5,700	−79	−24	−58	−1,600	−198	−142	−183
11‡	2,360	83	0	83	2,295	65	56	82	+65	+18	−56	+1	+65	+18	−56	+1
*	3,187	69	0	69	3,830	115	53	104	−643	−46	−53	−35	−578	−28	−109	−34
*	4,012	197	0	197	3,052	113	36	111	+960	+84	−36	+86	+382	+56	−145	+52
*	4,930	205	0	166	4,850	127	43	130	+80	+78	−43	+36	+462	+134	−188	+88
	1,782	24	41	30	1,697	115	38	105	+85	−91	+3	−75	+547	+43	−185	+13
12	340	0	0	0	810	31	24	22	−470	−31	−24	−22	−470	−31	−24	−22
	1,525	53	78	62	1,745	58	56	60	−220	−5	+22	+2	−690	−36	−2	−20
	1,030	91	61	83	1,310	87	50	83	−280	+4	+11	0	−970	−32	+9	−20
	1,585	66	67	62	1,765	123	61	119	−180	−57	+6	−57	−1,150	−89	+15	−77
	2,606	88	88	80	2,016	123	67	126	+590	−35	+21	−46	−560	−124	+36	−123
13‡†	2,769	80	0	80	2,602	187	74	177	+167	−107	−74	−97	+167	−107	−74	−97
*	3,497	252	0	252	3,820	267	78	250	−323	−15	−78	+2	−156	−122	−152	−95
*	3,736	308	0	308	3,495	218	67	233	+241	+90	−67	+75	+85	−32	−219	−20
*	3,944	308	0	308	3,370	200	49	215	+574	+108	−49	+93	+659	+76	−268	+73
*	3,485	185	0	185	3,315	191	39	199	+170	−6	−39	−14	+829	+70	−307	+59

(*x*) The water intake includes an allowance for endogenous water production, calculated as described in *Methods* (pp. 379–80).
(*y*) The output includes the insensible loss of water and the assumed loss of electrolytes from the skin (see *Methods*, pp. 379–80).
* This refers to 24-hour balance periods when intake and output were larger than normal, but the change in balance was small (see text).
† This refers to 24-hour balance periods when the change of external balance was large.
‡ In these cases the cumulative potassium balances were greater than −140 mM.

and when the change of balance was large. A final comparison is possible between patients in whom the change in potassium balance at the end of the balance study was small, and a group in whom it was larger. In seven subjects,



Changes in serum-sodium levels after trauma.

marked ‡ in Table II, the average loss of potassium at the end of the study was 203 mM. (range −142 to −307 mM.). In the remaining six subjects the average potassium loss was 50 mM. (range +15 to −74 mM.).

Serum-sodium levels after trauma. In the accompanying figure the observed changes in serum-sodium level in Groups A and C are plotted. With one exception (Case 12) the tendency over the period of observation was for the serum-sodium to decrease. The external sodium balance was positive in six cases, and negative in four (Cases 1, 5, 6, 12). Thus these observations confirm the view

TABLE III

Predicted minus Observed Total Cation Level in the Extracellular Fluid [B] (mM. per Litre)

	Days after operation or trauma									
Case number	*0–last day**	*1*	*2*	*3*	*4*	*5*	*Mean*	*Standard error of mean*	*t*	*P*
1	−0·9	0	+0·7	+0·4	−3·1	+1·3	−0·1	0·8	0·1	$0·2 < P$
2	+0·7	+0·8	−0·6	0	+2·0	−0·8	+0·3	0·5	0·6	$0·2 < P$
3	+3·0	G†	−2·3	+3·0	−1·2	+3·4	+0·7	1·4	0·5	$0·2 < P$
4	+2·0	G†	+2·5	−0·1	+0·9	−3·3	0	1·2	0	$0·2 < P$
5	−1·0	−2·6	+1·5	+0·3	..	..	..	..	..	..
6	−2·1	−1·3	+0·2	−0·6	..	..	..	..	..	..
7	+0·4	G†	−0·5	+0·7	..	..	..	..	..	..
8	+2·1	+2·1	..	..	..	..	..	..	..	..
9	−3·5	+1·2	−1·2	−0·8	−0·9	−1·0	−0·5	1·1	0·5	$0·2 < P$
10	−0·4	+1·4	−0·3	..	..	..	..	..	..	..
Mean of Cases 1–10	0	+0·2	0	+0·4	−0·5	−0·1	..	..	..	..
Standard error of mean	0·6	0·7	0·5	0·4	0·9	1·1	..	..	..	..
t	0	0·3	0	1·0	0·6	0·1	..	..	..	..
P	$0·2 < P$	$0·2 < P$	$0·2 < P$	$0·2 < P$	$0·2 < P$	$0·2 < P$	..	..	..	..
11	−1·1	−0·5	+0·9	+1·1	−0·4	−1·2	0	0·5	0	$0·2 < P$
12	−2·4	−0·9	+1·5	−3·4	+1·4	−1·3	−0·5	0·7	0·7	$0·2 < P$
13	−0·1	+1·5	+0·9	0	−0·6	−1·6	0	0·5	0	$0·2 < P$
Mean of Cases 1–13	−0·3	+0·2	+0·3	+0·1	−0·2	−0·6	..	..	..	..
Standard error of mean	0·4	0·5	0·4	0·5	0·6	0·7	..	..	..	..
t	0·7	0·4	0·7	0·2	0·3	0·1	..	..	..	..
P	$0·2 < P$	$0·2 < P$	$0·2 < P$	$0·2 < P$	$0·2 < P$	$0·2 < P$	..	..	..	..

Mean of all values for predicted minus observed [*B*] for each 24-hour period = 0 (standard deviation = 1·5) mM. per litre.

* This value is derived from the progressive balance figures from the beginning to the end of the balance study (see *Methods*), and it is not included in the mean difference shown in the right-hand column.

† G refers to the occurrence of hyperglycaemia. These days are excluded from the calculation (see text).

that the serum-sodium level tends to fall after trauma (from operation or otherwise), and that this occurs even when sodium balance is positive—the sodium paradox of Moore and Ball (1952).

Comparison of the predicted and observed total cation levels in the extracellular fluid. In Table III are given the differences (in mM. per litre) between the predicted and observed total cation concentrations in the extracellular fluid for all the 24-hour balance periods in all the patients. (Three values in Day 1 are excluded because of the occurrence of hyperglycaemia.[4]) The mean of all these values for the differences is zero, and hence there is no consistent error in the prediction of $[B]$. The standard deviation of the values of the differences is 1·5 mM. per litre, so that two-thirds of the predictions are within 1·5 mM. per litre of the observed level. In the surgical cases alone (Groups A and B), on each of the first five days after operation, the mean value for predicted minus observed $[B]$ for each 24-hour period does not differ significantly from zero ($0{\cdot}2 < P$). The same conclusion applies if the surgical and medical cases are taken together. In the eight cases studied for five days (including the three medical cases) the mean value for predicted minus observed $[B]$ for the five 24-hour periods in each subject does not differ significantly from zero ($0{\cdot}2 < P$). Table III also records the values for predicted minus observed $[B]$ found by using the progressive balance figures for the whole period of three or five days. The mean of all the values of the differences is −0·3 mM. per litre, a figure not differing significantly from zero ($0{\cdot}2 < P$). This corroborates the belief that there is no systematic error in the method of prediction.

When the accuracy of prediction is compared as between the 26 periods with small intake, output, and balance changes, and the 16 periods (marked by an asterisk in Table II) with large intake and output but small balance changes, no statistically significant difference is found. This indicates that the balance techniques employed were not subject to significantly large systematic errors. The predicted change in $[B]$, and the difference between predicted and observed $[B]$, for the 10 periods in which balance changes were greatest, are listed in Table IV. The mean value for the differences is +0·7 mM. per litre, which does not differ significantly from zero ($0{\cdot}2 < P$). The standard deviation is identical with that found for all the values of this difference in all the cases, showing that the accuracy of prediction is almost as good when the change in $[B]$ is large as when it is small. From Table IV it can be observed that both large increases and decreases in the value of $[B]$ were found. Although the results are too few to be examined statistically, there appears to be no significant difference in the accuracy of prediction in the two groups.

[4] In discussing the osmotic theory of prediction, attention was drawn to the fact that hyperglycaemia causes serum-sodium to fall, because of the osmotic effect of the glucose which draws water from the cells (Wynn, 1954). In three instances, all on the first day after operation, there was hyperglycaemia, the increase of serum-glucose above the previous level being 315, 260, and 152 mg. per 100 ml. The corresponding serum-sodium levels were considerably lower than had been predicted, and this could reasonably be attributed to the hyperglycaemia. The hyperglycaemia occurred in spite of precautions taken to avoid it, and this fact emphasizes the importance of taking it into account as a possible cause of hyponatraemia.

When the seven subjects with maximum loss of potassium (marked ‡ in Table II) are compared with the six subjects with minimum loss, no statistically significant difference in the accuracy of prediction is found ($0{\cdot}2 < P$). This supports the assumption, used in deriving the formula of prediction, that potassium has the same osmotic value as sodium in the relationship between water and total electrolytes. In other words, potassium depletion is an important factor

TABLE IV

Predicted Change in [B], and the Difference between Predicted and Observed [B], in 10 Instances in which the Change of Water and Electrolyte Balance was Greatest

Case number	*Day*	*Predicted [B] (mM./l.)*	*Predicted minus observed [B] (mM./l.)*
1	1	−4·3	0
2	2	−4·5	−0·6
3	5	+7·4	+3·4
8	1	+12·8	+2·1
9	1	−19·5	+1·2
	2	+10·7	−1·2
	3	+9·6	−0·8
10	1	−23·0	+1·4
	2	+21·4	−0·3
13	1	−5·7	+1·5
Mean (disregarding sign)		11·9	Mean +0·7
		Standard error of mean	= 0·5
			$t = 1{\cdot}4$
			$0{\cdot}2 < P$

in the development of a low serum-sodium level. The clearest examples of this effect are Cases 3 and 13 (Table II and Figure). In these patients serum-sodium decreased by about 8 mM. per litre, and this decrease could be accounted for predominantly by the large negative potassium balance. The mechanism whereby loss of potassium contributes to extracellular hypotonicity cannot be defined from these studies. The possibilities are that depletion of intracellular osmotically active solutes releases water from the cells, or that potassium is replaced by sodium. Evidence based upon changes of chloride balance, serum-chloride levels, the serum chloride/sodium ratio, and the assumption that all chloride is extracellular, suggests that on the average, in our patients, only about 40 mM. of sodium entered cells in exchange for potassium. But the evidence is so indirect that it is not worth while to give in detail the figures upon which this calculation is based.

The results of the balance studies show that after trauma the level of total cation which is observed in the serum is predictable according to simple osmotic theory, and this applies whether the level is falling (because of water retention or cation depletion) or rising (because of water loss or cation excess).

Water retention after trauma. In eight of the 10 cases in Groups A and C the water balance was positive at the end of the period of observation (Table II). The average water retention in these eight cases was +478 ml., the average sodium balance +59 mM., and the potassium balance −151 mM. Thus, on the average, very little more water was retained than would be expected from the

sodium balance, but when the loss of potassium is taken into account the excess of water relative to total electrolytes becomes obvious. Because of this actual and relative excess of water the serum-sodium level fell. The serum hypotonicity, together with a positive water balance, is evidence of the existence of an antidiuretic mechanism not determined by extracellular osmolarity. In a normal person a water load sufficient to reduce serum osmolarity by about one per cent. is followed by a water diuresis due to inhibition of the secretion of antidiuretic hormone (Verney, 1947–8). After trauma, surgical or non-surgical, this diuretic mechanism is altered, and lower levels of serum osmolarity are permitted without a profuse water diuresis occurring. The reasons for this alteration are obscure. It is known that for 24 to 36 hours after trauma there is usually an oliguria, and the urine is of high osmolarity. This is probably due to excessive secretion of antidiuretic hormone (Theobald and Verney, 1935; Le Quesne and Lewis, 1953; Eisen and Lewis, 1954), but renal haemodynamic changes may also play a part. Many stimuli provoke the secretion of antidiuretic hormone, including pain, fear, anger, and drugs such as anaesthetics, morphia, pethidine, the barbiturates, nicotine, and acetylcholine. Adrenocortical insufficiency, anaemia, and hypoproteinaemia may also provoke antidiuretic responses. But the condition of serum hypotonicity and water retention described here cannot certainly be attributed to any of the causes mentioned above. First, it may be seen several days after the trauma occurs, even into the second week (Wynn and Rob, 1954). Second, there is not necessarily an oliguria, but rather a restricted urine output, which does not exceed about three litres a day. Third, there may be no evidence of a large reduction in glomerular filtration rate, or of an excessive secretion of antidiuretic hormone, at any rate as assessed by the blood-urea level and the urine specific gravity. The following description exemplifies these points.

In Case 3 blood taken at the beginning of the fifth day after an uncomplicated partial gastrectomy had a serum-sodium level of 132 mM. per litre, which was 8·5 mM. per litre lower than the level before operation (Fig. 1). The progressive water balance at this time was +2,061 ml., the sodium balance +116 mM., and the potassium balance −148 mM. The preceding 24-hour urine volume was 2,110 ml., the specific gravity 1,003, and the osmolarity 116 mM. per litre. The urine osmolarity was not directly determined, but was assumed to be equal to $(NH_4+Na+K)\times 2+$urea (mM.). This calculation gives a figure which is close enough for present purposes. Serum non-protein nitrogen was 15 mg. per 100 ml., which was 10 mg. per 100 ml. lower than the level before operation. There was a large negative nitrogen balance of 32·5 gm., so that the low level of serum non-protein nitrogen can be taken as reasonable evidence of a fairly normal glomerular filtration rate. The low urine specific gravity and osmolarity are evidence against an excessive secretion of antidiuretic hormone. Nor can anaemia or hypoproteinaemia be invoked to account for the restricted output of urine, since the haemoglobin was 11·4 gm. per 100 ml. and serum-protein 6·15 gm. per 100 ml.

From this example, and others which have been described previously (Wynn and Rob, 1954), it seems clear that osmoregulation by the kidneys is abnormal

after trauma. It is this alteration in osmoregulation, permitting water retention, which underlies the development of serum hypotonicity after trauma.

Changes in serum-chloride, -potassium, and -bicarbonate after trauma. Serum-chloride. The changes in serum-chloride after trauma closely followed the sodium levels. This is shown by the fact that the ratio of Cl to Na in the serum was not significantly altered at the end of the study, compared with the initial value. Nor was there a significant change in the ratio at the time of the maximum decrease of sodium.

Serum-potassium. Dudley, Boling, Le Quesne, and Moore (1954), and Wilson, Edelman, Brooks, Myrden, Harken, and Moore (1954), observed an increase in serum-potassium at the time when the serum-sodium level was low, and ascribed special significance to this 'Na/K shift'. Of the nine cases in Groups A and C in which the serum-sodium level fell, serum-potassium decreased in seven cases (mean −0·41 mM. per litre) and increased in two (+0·4 and +0·2 mM. per litre). In the two cases of severe serum hypotonicity in Group B (Cases 9 and 10) the serum-potassium level fell at the height of the hyponatraemia (−0·3 and −1·1 mM. per litre). Therefore, in the present series, the 'Na/K shift' described by Dudley, Boling, Le Quesne, and Moore was not observed.

Serum-bicarbonate. In nine cases in Groups A and C (excluding Case 5 because of loss of acid gastric juice) there was no consistent change in serum-bicarbonate levels from the beginning to the end of the study. The average change was a fall of 0·16 mM. per litre (range +2·7 to −2·9 mM. per litre). The seven cases of maximum potassium loss warrant special study. Case 5 is excluded (see above), and also Case 9, in which bicarbonate analyses were not done. Of the remaining five cases (3, 4, 10, 11, and 13), serum-bicarbonate decreased in four (mean 2·1 mM., range 2·9 to 0·7 mM. per litre), and increased in one (+1·5 mM. per litre). The results indicate that in these cases potassium depletion was not associated with extracellular alkalosis, as has been reported previously (Cooke, Segar, Cheek, Coville, and Darrow, 1952). This finding makes the movement of significant amounts of H^+ into cells unlikely, and hence this factor does not introduce an error into the osmotic calculations (see *Theory*).

Discussion

The studies reported here show that after trauma (surgical and non-surgical) the extracellular fluid osmolarity (derived from the serum-electrolyte levels) is not significantly different from that which would be predicted if the cells of the body behave volumetrically as perfect osmometers, as postulated by the Gamble hypothesis. This conclusion holds even when the change in osmolarity is large, and whether the change is a decrease or an increase in osmolarity. Our results therefore support classical views on the osmotic behaviour of cells, a subject which is considered controversial at the present time (Robinson, 1954; Conway and McCormack, 1953). Concepts such as the 'osmotic inactivation' of cell-solutes (Elkinton, Winkler, and Danowski, 1944–5), or the movement of hypotonic fluid from the cells to the extracellular fluid after trauma, thus setting up

a sustained osmotic gradient across the cell-membrane (De Cosse, Randall, Habif, and Roberts, 1956) are weakened by observations such as ours. These concepts imply that extracellular-fluid osmolarity is significantly different from that predicted by simple osmotic theory from the change in water and electrolyte balance; and in our cases this difference did not occur. These conclusions are based upon the study of 13 patients, only eight of whom were studied for as long as five days after the operation or the initial trauma. But we found nothing to suggest that more severe trauma would have resulted in different findings, and in other cases (not reported), in which the patients were wasted by disease, more limited observations have confirmed the present thesis. Further, the present study includes only two cases of severe hypotonicity, but we have observed several others in which the serum hypotonicity seemed to accord with the balance data available (Wynn and Rob, 1954).

It is worth while to consider briefly possible reasons for the disagreement between our conclusions and those of other workers. In some accounts total body-water and insensible loss of water were not measured, but assumed values were used. None of the studies reported so far appears to have taken possible hyperglycaemia into account, nor to have allowed for endogenous water production. But by far the most important factor is probably that insufficient attention has been paid to the osmotic effects of loss of potassium. This factor was disregarded by Goodyer and Glenn (1955), and its effects were not assessed quantitatively by Dudley, Boling, Le Quesne, and Moore (1954), nor by Wilson, Edelman, Brooks, Myrden, Harken, and Moore (1954). Our results show that loss of potassium from the cells may be an important contributory cause of serum hypotonicity. The results are consistent with the view that potassium and sodium have the same osmotic value. When sodium is retained, its osmotic effect may be offset by loss of potassium. When water is retained, and both sodium and potassium are lost, the effects on serum hypotonicity are additive, and serious dilution of the body-fluids may ensue. This may account for those cases of hypotonicity after operation, with severe symptoms, described by Zimmermann and Wangensteen (1952), who were unable to explain their findings on the basis of water retention alone.

Our results, in keeping with those of other workers, confirm the belief that water retention is the major cause of serum hypotonicity after trauma. It has been pointed out above, and elsewhere (Wynn and Rob, 1954), that disordered renal function, in the sense of a greatly lowered glomerular filtration rate, cannot account for it. This implies that tubular reabsorption of water is excessive. A possible mechanism may follow from the views of Leaf and Mamby (1952), who suggested the existence of 'volume receptors', which react to changes in the volume of the body-fluids, or some function of volume, and act through the neurohypophyseal-hypothalamic system. It is possible that trauma stimulates this volume-controlling mechanism to increase body-water by causing water retention. Its mode of action may be to reduce the sensitivity of the 'osmoreceptor' (Verney, 1947–8) to a falling serum osmotic pressure. Renal regulation of the body-fluids would now occur about a serum-sodium level lower than

usual, and with a larger than usual total volume of body-water. The volume and composition of the urine would then reflect the new levels. The restricted output of urine with relatively low solute concentration, found in some of our patients, would be explicable on such a basis. But, in spite of the experimental and clinical evidence which has been adduced to support the theory, the existence of 'volume receptors' remains hypothetical (Robinson, 1954).

The clinical significance of our results lies in the greater certainty with which changes in serum osmolarity can be assessed and treated. For practical purposes serum-sodium levels can be used to depict the serum osmolarity, since changes in serum-potassium are usually small. Low serum-sodium levels, and the reverse, are common clinical findings. If treatment is required, the relative amount of water and electrolytes necessary to correct the disorder can be derived from the osmotic considerations described in this paper. Depletion of intracellular potassium commonly contributes to the cause of serum hypotonicity, and this should be taken into account in prescribing treatment.

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Summary

1. Patients were studied for up to five days after the trauma of a surgical operation (10 cases), coronary occlusion (two cases), and dissecting aortic aneurysm (one case).

2. Serum osmolarity, as measured by serum total cation levels, was followed daily, as well as the daily water and electrolyte balance.

3. Characteristically, serum hypotonicity, shown by a low serum total cation level, developed after trauma. Instances in which serum osmolarity increased were also observed, and sometimes there was no change. When the observed change in serum total cation level from day to day was compared with the change which would have been predicted by simple osmotic theory, from the water and electrolyte balance, no statistically significant difference was found.

4. These results support the views of Gamble that, taking the body-cells as a whole, osmotic adjustments occur by the redistribution of water and electrolytes according to the concentrations of the osmotically-active solutes on both sides of the cell-membrane.

5. Our results show that the potassium balance plays an important part in determining serum osmolarity, although it is often overlooked in this context. In our cases the osmotic value of sodium and potassium was the same.

6. Serum hypotonicity following trauma is largely due to water retention, the reason for which at the present time cannot be explained.

7. The clinical significance of these results is discussed.

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JEJUNAL BIOPSY AFTER PARTIAL GASTRECTOMY[1]

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With Plates 37 to 40

Changes in the gastric mucosa resulting from gastrectomy have been reported (Joske, Finckh, and Wood, 1955), but little is known about the effects of this operation on the small intestine, and the histological appearances of the jejunal mucosa after gastrectomy have not been studied. Joske, Finckh, and Wood (1955), using a biopsy tube of their own design, found in their series of gastric biopsies that pathological changes, consisting of either superficial gastritis or gastric atrophy, were present in 68 per cent. of 44 specimens taken from patients who had had either gastrectomy or gastroenterostomy. Palmer (1953) also noted a high incidence of gastritis after gastrectomy.

Both iron-deficiency anaemia and steatorrhoea are well-recognized complications of gastrectomy. The reasons for these developments are not well understood, but it is known that it is the mucosa of the small intestine that is concerned with the absorption of both iron and fats (Hahn, Bale, Ross, Balfour, and Whipple, 1943; Endicott, Gillman, Brecher, Ness, Clarke, and Adamik, 1949; Stewart, Snowman, Yuile, and Whipple, 1950). It is also known that iron-deficiency anaemia is often associated with gastric atrophy (Davidson and Markson, 1955). The present investigation was undertaken to determine whether any recognizable changes in the jejunal mucosa commonly occurred after gastrectomy, and whether the development of either iron-deficiency anaemia or of steatorrhoea could be correlated with any histological abnormalities. No systematic biopsy studies of the jejunal mucosa have hitherto been made. Badenoch, Evans, Richards, and Witts (1955) obtained biopsies of jejunal mucosa from two patients with megaloblastic anaemia after gastrectomy. Shiner (1956) performed a series of duodenal biopsies, and in one patient, who had previously undergone a Polya gastrectomy, the tube was passed into the jejunum. The appearance of the mucosa was very similar to that of the third part of the duodenum. These were, however, isolated observations.

Patients Investigated and Methods

The study we report deals first with the presumably normal jejunum in 11 patients at the time of gastrectomy, and secondly with the appearances of

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the jejunum as seen in 31 biopsies taken at varying intervals after the operation of partial gastrectomy.

Clinical cases. Eleven biopsies were taken at the time of operation from patients undergoing subtotal gastrectomy. The specimens were taken from jejunum immediately distal to the anastomosis; care was taken in handling them, in order to preserve the normal appearance of the tissue. The Wood's tube was passed in 32 patients who had previously undergone gastrectomy. In none of them was there any evidence of recurrent ulceration, but several were suffering from anaemia or steatorrhoea. The specimens were all obtained from the efferent loop of jejunum. Of 32 jejunal biopsies attempted, there were three failures. In one case only gastric mucosa was obtained; in one the tube could not be passed through the pylorus. In one instance there was no apparent cause for the failure. A satisfactory jejunal biopsy was obtained in 29 of the 32 patients examined. Two additional jejunal specimens were obtained in two post-gastrectomy patients who had further abdominal operations. All patients remained in hospital for 24 to 48 hours after the biopsy; the pulse was charted at regular intervals. A drink of water was allowed one hour after the biopsy. In one patient, a man of 60, there was a transient attack of auricular fibrillation. Otherwise no untoward effects were noted. In 12 cases the faeces were examined for occult blood during the week after discharge from hospital; the results were consistently negative. There were no immediate gastrointestinal complications in the patients who underwent gastrectomy, except in one case. This patient, a man of 46, had a Polya gastrectomy on October 24, 1955 for a long-standing duodenal ulcer. On November 2, 1955 he developed an angular stomatitis and a red, 'beefy', sore tongue with superficial ulceration, and began to pass frequent, loose, pale motions. The oral abnormalities subsided without therapy in three weeks, and the motions returned to normal in about six weeks. On account of the oral lesions jejunal biopsy was not possible until three months after gastrectomy; the appearance of the jejunum is described below.

Method of jejunal biopsy in post-gastrectomy patients. The biopsy tube comprises a length of Bowden wire, covered by plastic in order to make an airtight tube (Joske, Finckh, and Wood, 1955). The outer diameter of the tube is $\frac{1}{4}$ inch. A wire passes from the proximal end down the length of the instrument, and operates a terminal knife-blade, which is cylindrical and is encased in a stainless steel chamber. A fragment of mucosa can be sucked through a lateral hole in the chamber by exerting suction through a lateral opening at the proximal end of the tube. The knife-chamber contains a terminal screw, which is released in order to change the blade, and to remove the excised fragment of mucosa. The length of the tube is 100 cm. and there are marks at 45, 55, and 65 cm. from the lateral hole. The patient is fasting, and it is not necessary to empty the stomach. A gargle is given with 2 ml. of 1 per cent. amethocaine solution. The patient is placed in the left lateral position on a screening table in the X-ray department, and the tube is passed by exerting gentle pressure on its proximal end. When the stomach is reached the patient is turned on his back, and the screening table is tilted to the horizontal position. The tube is guided under radiological control

into the approximate position of the efferent loop of jejunum. When this is achieved, suction is applied to the proximal end of the tube with a 20 ml. syringe and rubber tubing. The wire is operated to pull up the blade, which cuts off the fragment sucked into the lateral hole of the knife-chamber. The operation is repeated after withdrawing 2 to 3 cm. and rotating 180 degrees. Two samples of mucosa are obtained if possible, the first as far down the jejunum, and the second as near the stoma as possible (Plate 37, Figs. 1 and 2).

In order to confirm the fact that the tube is in the efferent loop of jejunum, the patient is required to swallow a mouthful of barium, and a film is taken. It is important to take the biopsy specimens before the barium is given, as the paste may interfere with the action of the knife. The tube is finally withdrawn and wiped clean of barium. The terminal screw is removed, and the fragments are placed immediately in 10 per cent. formol-saline.

Histological methods. The biopsy specimens consisted of small disks of mucosa, in most cases about 0·3 cm. in diameter, when they were taken by Wood's tube. In the case of the biopsies taken at the time of gastrectomy the material consisted of a strip of jejunum, 1·5 to 3 cm. in length, usually including both circular and longitudinal muscle coats in addition to the mucosa and submucosa. They were fixed in 10 per cent. formalin, embedded in paraffin, and cut in vertical sections. All specimens were stained with Ehrlich's haematoxylin and eosin. This haematoxylin stains the mucin of intestinal goblet-cells. Other staining methods used included Masson's trichrome, Perl's reagent and van Gieson's stain, phosphotungstic-acid-haematoxylin, Southgate's mucicarmine, phloxine and tartrazine, a modified Bielschowsky method for reticulin, and Fontana's method for argentaffin cells.

Results

The histology of the normal human jejunal mucosa has not been extensively studied. Post-mortem specimens are often uninformative on account of the rapid autolysis that takes place after death. The absence of detailed information regarding the histological appearances in health suggested the need to obtain samples of jejunal mucosa from patients who have not already undergone gastrectomy. Accordingly, a strip of proximal jejunum was removed at the time of operation from patients who were undergoing gastrectomy for peptic ulcer. These specimens, while not from normal subjects in a strict sense, were taken from jejunal mucosa situated in its normal position in relation to the stomach and duodenum, protected from direct contact with the gastric contents, and from patients who showed no evidence of intestinal malabsorption.

Normal jejunum. Our account is based on the almost identical appearances seen in the 11 biopsies taken at the time of gastrectomy. The tissues, fixed very shortly after excision, showed excellent preservation. The villi are long, slender, and finger-like, and make up about two-thirds of the thickness of the mucosa. Between the villi the mucosa dips down to form short, straight, tubular glands; the rounded blind ends of these glands form the crypts of Lieberkühn, lying in

contact with the thin but clearly defined muscularis mucosae. The tubular glands and the intervening stroma constitute about one-third of the thickness of the mucosa (Plate 38, Fig. 3).

The surface epithelium (Plate 38, Fig. 4) consists of a single layer of epithelial cells, with an oval nucleus situated at the pole of the cell furthest from the lumen. The cytoplasm is deeply eosinophilic, and bordering the lumen there is a brush-border of tiny cytoplasmic filaments projecting vertically from the cell surface. At fairly regular intervals (at about every fifth cell) an epithelial cell is seen containing a large, rounded mass of mucin (a 'goblet-cell'). The mucin is of 'intestinal' type, staining blue with Ehrlich's haematoxylin. Surface epithelium and goblet-cells line the villi, and also line the superficial parts of the tubular glands (Plate 38, Fig. 5). The cells lining the crypts show very numerous mitoses; a transverse section through the lower half of a crypt will usually show at least one mitotic figure. Mitoses are not seen in the epithelium of the villi. At the lower, rounded ends of the crypts are found groups of epithelial cells whose cytoplasm contains large numbers of coarse granules, which stain brilliantly red with eosin. These are the Paneth cells, characteristic of the small intestinal mucosa; they are believed to be concerned with the production of the digestive enzymes of the succus entericus. Most of the cells are full of granules, but sometimes large 'empty' cells are seen, containing only scanty granules. The cytoplasm of the Paneth cells extends up to the lumen of the crypt (compare the oxyntic cells of gastric mucosa). Argentaffin (Kultschitzky) cells are present in the crypts. They are not easily recognized in haematoxylin-and-eosin sections, but in silver preparations the argentaffin granules show up very distinctly (Plate 39, Fig. 6). The cells are usually situated towards the outer side of the crypt, and often do not appear to be in contact with the lumen.

The stroma of the jejunal mucosa is fairly abundant; it consists of a very delicate connective-tissue network, in which thin-walled blood-vessels can be seen. The stroma always shows a considerable population of histiocytes, lymphocytes, plasma cells, and eosinophils, compared with the relatively scanty and non-cellular stroma of gastric mucosa and its much more closely packed glands (Plate 39, Fig. 7). Occasionally a small endothelium-lined channel can be seen running vertically through the centre of a jejunal villus. An occasional strand of smooth muscle may also be seen, sometimes branching off from the muscularis mucosae, and running vertically up the core of a villus. Lymphoid follicles are not usually present in the jejunum, but sometimes ill-defined aggregations of lymphocytes, without follicular pattern, are present in the deepest layer of the mucosa; at times they appear to interrupt, or perhaps to displace, the fibres of the muscularis mucosae. The latter shows no special features; it appears to vary somewhat in thickness, probably because of the different planes in which it is cut. The plane of section also considerably affects the apparent length and thickness of villi and crypts. The description given here corresponds to the picture seen in sections vertical to the lumen.

The jejunum after gastrectomy. In 23 of the 31 specimens taken at various intervals after gastrectomy (Plate 39, Fig. 8) the appearances were entirely

similar to those seen in the 11 examples taken at operation, and may be classed as normal. In particular, the number and distribution of mucus-containing goblet-cells, Paneth cells, and Kultschitzky cells, did not differ from those seen in the pre-gastrectomy specimens. It is clear that in these cases the short-circuit had produced no detectable change in the histological appearance in the jejunum. The appearance was also normal in the patient who had developed transitory glossitis and diarrhoea immediately after gastrectomy. In eight cases in which gastrectomy had been done, certain histological changes were seen in the jejunum. (1) *Hyperaemia and oedema of villi.* In four such cases single villi, or a small group, were increased in thickness, and showed oedema of the stroma, particularly at their free ends (Plate 40, Fig. 9). In many cases the epithelial cells at the tip of the villus were also partly separated by intra-epithelial oedema. The affected villi showed prominent, dilated capillaries, filled with red cells. It is possible that these changes represent part of a physiological cycle of activity on the part of the villi. It has been shown in dogs (Kokas and von Ludány, 1930) that the intestinal villi undergo a cycle of contraction and relaxation, and that each villus appears to act quite independently of its neighbours. Possibly these hyperaemic, oedematous villi are those in which active absorption from the lumen is taking place; it is not justifiable to label such changes as pathological. (2) *Atrophic changes in villi.* In two biopsy specimens mild atrophic changes were seen. In these cases all the villi were somewhat shorter and 'stubbier' than normal (Plate 40, Fig. 10), and tapered slightly towards the tip, in contrast to the normal villi, which often showed a slight widening towards the tip. Goblet-cells were scanty in these cases, but no alteration was seen in the Paneth cells or other elements. (3) *Inflammatory changes.* There was an increase in the cellular content of the mucosal stroma in one patient, who had steatorrhoea after gastrectomy. The infiltrating cells comprised histiocytes, lymphocytes, and eosinophil polymorphs, and seemed much more densely collected than in any normal specimen. This picture represents at most only a mild degree of inflammation, and is quite distinct from the severe changes which were seen in one patient who had a stomal ulcer. For comparison these features are illustrated in Plate 40, Fig. 11.

Histological Appearances of the Jejunum in the Different Clinical Groups (Table I)

Before gastrectomy identical mucosal patterns were seen in all 11 cases, and have been taken as normal.

Non-anaemic patients after gastrectomy. Jejunal biopsies were obtained from nine patients who had a normal blood count (haemoglobin level higher than 12·6 gm. per 100 ml.), within three months after subtotal gastrectomy. The mucosa was normal in six patients. There were vascular changes, namely hyperaemia and oedema, in two patients. A jejunal specimen obtained at operation in one patient, who was undergoing a second gastrectomy for stomal ulcer, showed changes indicating hypertrophic jejunitis.

Patients with iron-deficiency anaemia after gastrectomy. Biopsy of the jejunal mucosa was performed by using the Wood's tube in 17 instances. In 14 cases no abnormality was observed. Two showed vascular changes, and in one jejunal atrophy was seen. The haematological and clinical details are shown in Table II, and it is evident that the anaemia is not regularly associated with changes in the jejunal mucosa.

TABLE I

Analysis of Jejunal Histology in 11 Pre-Gastrectomy and 31 Post-Gastrectomy Patients

	Total	*'Normal'*	*Hyperaemia with or without oedema*	*Atrophic change*	*Jejunitis*
Pre-gastrectomy . .	11	11	0	0	0
Post-gastrectomy: .	31	23	4	2	2
No anaemia . .	9*	6	2	0	1
Anaemia . . .	17	14	2	1	0
Steatorrhoea . .	5*	3	0	1	1

* Including one operation specimen.

Steatorrhoea after gastrectomy. The appearance of the jejunal mucosa was studied in five patients with steatorrhoea. Four of these specimens were obtained by jejunal biopsy; a fifth was obtained at operation, when a Polya gastrectomy was converted into a Billroth I gastrectomy. Steatorrhoea in these five patients was confirmed by fat-balance tests. The results are shown in detail in Table I. Three biopsy specimens showed a normal appearance, one showed atrophic changes, and one showed jejunitis. These results indicate that, although moderate steatorrhoea is present in some patients after gastrectomy, there is in this disorder no consistent evidence of inflammatory or atrophic changes in the jejunum.

Discussion

The technique of jejunal biopsy in patients who have had subtotal gastrectomy has been described. It provided satisfactory histological material in 91 per cent. of the cases examined. This rate is comparable with the incidence of success in gastric biopsies. For example, Joske, Finckh, and Wood (1955) obtained a satisfactory specimen in 95 per cent. of their series of gastric biopsies. No serious complications were observed in the present series of 32 patients. The absence of the greater part of the stomach was associated with no constant histological change in the jejunal mucosa, in either the anaemic or the non-anaemic group of patients, and patients with a severe iron-deficiency anaemia showed normal histological appearances in the jejunum. There were jejunal mucosal abnormalities in only three out of 17 anaemic patients; in this respect the jejunal mucosa differs from the gastric mucosa. The interval between gastrectomy and biopsy did not seem to influence the incidence of jejunal changes. Davidson and Markson (1955), and Joske, Finckh, and Wood (1955), found that severe atrophic gastritis was commonly associated with iron-deficiency anaemia. Only two out of our five patients with steatorrhoea showed jejunal changes, one showing atrophy and the other jejunitis. Paulley (1954) described inflammatory jejunal

changes in idiopathic steatorrhoea. In the present group of patients, however, in whom steatorrhoea followed gastrectomy, no consistent inflammatory changes were seen. A transitory diarrhoea, angular stomatitis, and glossitis, were observed in one patient shortly after operation, and this clinical picture is

TABLE II

Seventeen Patients with Anaemia after Gastrectomy

Case number	Age (years)	Sex	Haematological data: Haemoglobin % (100% = 14·8 gm./100 ml.)	Red cells (millions/c.mm.)	Mean corpuscular haemoglobin concentration (%)	Mean corpuscular volume (c.μ)	Years since gastrectomy	Clinical abnormalities	Jejunum: histological appearance
1	43	F	48	3·2	22	82	7	Sore tongue, angular stomatitis	Normal
2	42	F	58	3·8	27	78	3	..	Oedema
3	42	F	42	3·2	24	85	5	..	Normal
4	41	F	55	3·5	27	85	7	..	Normal
5	42	F	42	3·6	21	81	5	Koilonychia, sore tongue, angular stomatitis	Atrophic
6	60	M	62	2·8	31	104	7	Koilonychia	Normal
7	65	F	70	3·5	28	87	2	..	Normal
8	50	M	65	3·5	28	98	3	..	Normal
9	60	M	82	5·0	30	80	7	..	Normal
10	45	F	68	3·8	29	84	7	Atrophic tongue, angular stomatitis	Normal
11	50	M	42	2·7	23	96	7	Atrophic tongue, brittle nails	Normal
12	45	M	64	4·0	26	76	3	..	Normal
13	50	F	66	3·4	26	108	9	Atrophic tongue, brittle nails	Normal
14	51	F	71	3·7	29	100	6	Brittle nails, transverse ridges	Normal
15	52	F	70	3·3	30	106	4	..	Normal
16	49	F	68	4·5	25	88	4	..	Normal
17	53	M	68	4·5	22	88	4	Brittle nails, atrophic tongue, angular stomatitis	Oedema

similar to the enteritis described by Riedel (1902), Penner and Bernheim (1939), and Fowler (1955) after surgery. No change in the jejunal mucosa was observed in our patient three months after gastrectomy. Evidently the occurrence of such an incident produces no permanent damage to the jejunum.

It is possible that a patchy jejunitis may have escaped the biopsy knife, but when two biopsy specimens of the jejunum were taken from the same patient they were closely similar. In anaemia and in steatorrhoea after subtotal gastrectomy no consistent histological change was found in the jejunal mucosa. Alterations in the structure of jejunal mucosa cannot, therefore, be an important cause of malabsorption of iron or fats after subtotal gastrectomy.

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Summary

1. A technique for jejunal biopsy in patients who have had gastrectomy is described. It was successful in 91 per cent. of the attempted biopsies. No serious complications resulted in 32 patients.

2. The histological structure of the normal human jejunum obtained at gastrectomy is described.

3. No histological changes were seen in 23 jejunal biopsies from 31 patients after gastrectomy.

4. Abnormal features in the biopsy series were hyperaemia and oedema of villi, mild atrophy of villi, and mild inflammatory infiltrations in the stroma of the jejunal mucosa.

5. Changes in the jejunal mucosa were seen in three out of nine non-anaemic patients within three months after gastrectomy.

6. Jejunal changes after gastrectomy were seen in three out of 17 anaemic patients, and in two out of five patients with steatorrhoea.

7. Iron-deficiency anaemia and steatorrhoea after gastrectomy cannot regularly be attributed to structural alterations in the jejunal mucosa.

8. The lapse of time between gastrectomy and the subsequent biopsy did not seem to influence the incidence of changes in the jejunum.

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FIG. 1. Showing the Wood's biopsy tube *in situ* in the efferent loop of jejunum prior to the biopsy

FIG. 2. Biopsy tube well down the efferent loop of jejunum

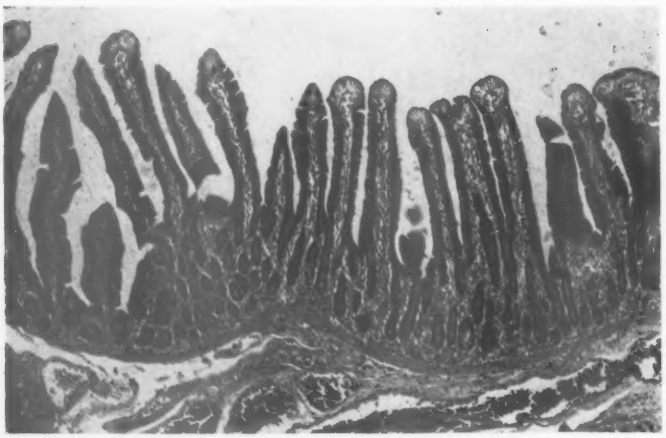

FIG. 3. A strip of jejunum taken at operation, showing normal histological appearances (haematoxylin and eosin, × 40)

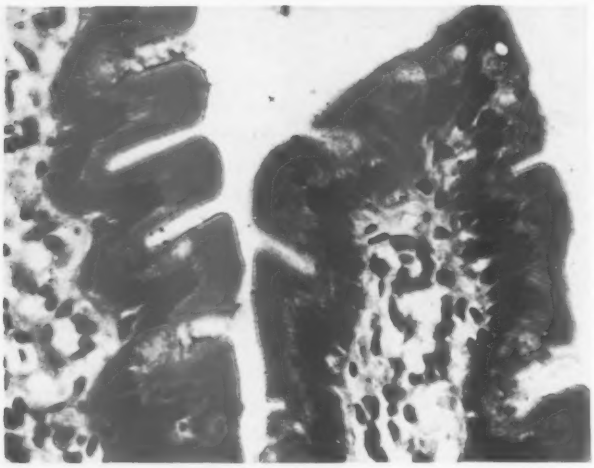

FIG. 4. Surface epithelium of villi, showing brush border and goblet-cells (haematoxylin and eosin, × 410)

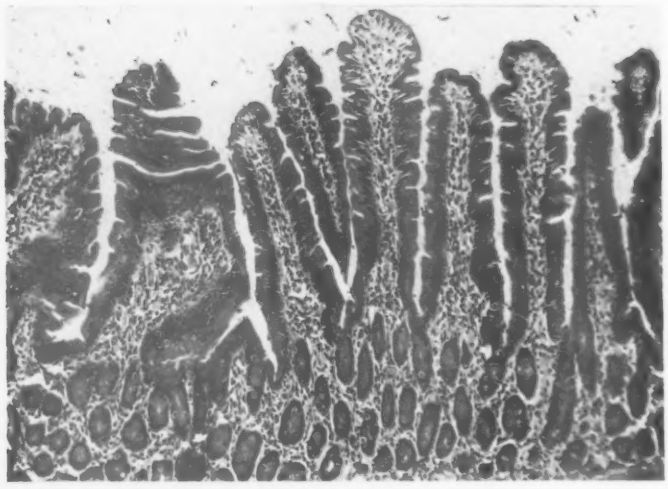

FIG. 5. Higher-power view of the same strip of jejunum as seen in Fig. 3 (haematoxylin and eosin, × 85)

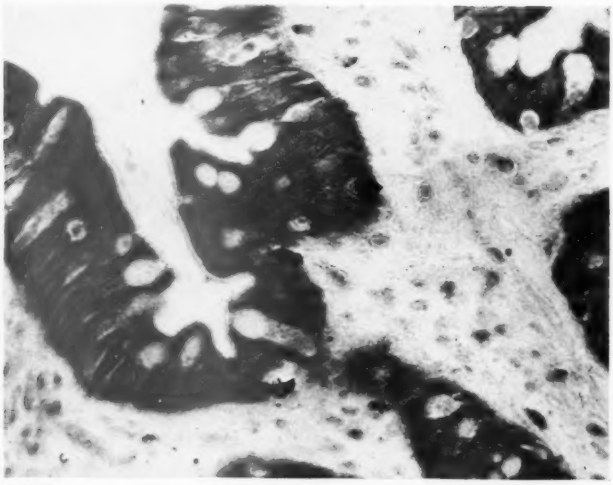

FIG. 6. Argentaffin (Kultschitzky) cells in the crypts of Lieberkühn. The argentaffin granules appear black in the photograph (Fontana–light green, × 460)

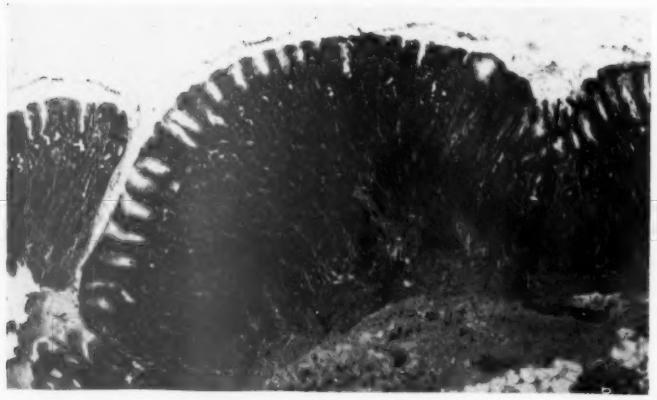

FIG. 7. A strip of gastric mucosa obtained at operation; compare with Fig. 3 (haematoxylin and eosin, × 40)

FIG. 8. Jejunal biopsy specimen taken with the Wood's biopsy tube after partial gastrectomy, to show the extent of tissue usually obtained. The specimen shows normal structure (haematoxylin and eosin, × 20)

FIG. 9. Biopsy of jejunum; thickening and oedema of villi are clearly shown on the right (haematoxylin and eosin, × 40)

FIG. 10. Biopsy of jejunum showing atrophic changes and 'stubby' villi (haematoxylin and eosin, × 40)

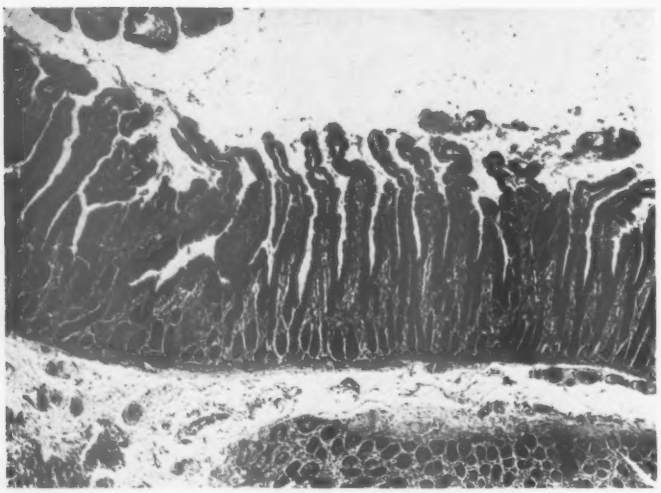

FIG. 11. A strip of jejunum from the vicinity of a stomal ulcer, showing lengthening of villi and cellular infiltration (haematoxylin and eosin, × 40)

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